Neonatal Therapeutic Hypothermia in Ireland

Annual Report | 2019

Aggregate Report 2016-2019

National Neonatal Therapeutic Hypothermia Development Project

Prepared by the National Clinical Programme for Paediatrics and Neonatology, the National Women and Infants Health Programme and the National Perinatal Epidemiology Centre

HSE

NATIONAL PERINATAL EPIDEMIOLOGY CENTRE

National Women & Infants Health Programme

National Clinical & Integrated Care Programmes

Person-centred, co-ordinated care

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List of Acronyms and Abbreviations

aEEG – Amplitude Integrated Electroencephalogram

APGAR – Appearance, Pulse, Grimace, Activity, Respiration

ARM – Artificial Rupture of Membranes

BAPM – British Association of Perinatal Medicine

BMI – Body Mass Index

CTG – Cardiotocograph

EDD – Estimated Due Date

FGR – Fetal Growth Restriction

FiO2 – Fraction of Inspired Oxygen

FVM – Fetal Vascular Malperfusion

GROW – Gestation Related Optimal Weight

HIE – Hypoxic Ischaemic Encephalopathy

IUGR – Intra Uterine Growth Retardation

MAVN – meconium-associated vascular necrosis

MDT – Multi-Disciplinary Team

MRI – Magnetic Resonance Imaging

MVM – Maternal Vascular Malperfusion

NCPPN – National Clinical Programme for Paediatrics and Neonatology

NE – Neonatal Encephalopathy

NG – Nasogastric Tube

NICU/SCBU – Neonatal Intensive Care Unit/ Special Care Baby Unit

NNEAG – National Neonatal Encephalopathy Action Group

NNT – Number Needed to Treat

NNTP – National Neonatal Transport Programme

NPEC – National Perinatal Epidemiology Centre

NRP – Neonatal Resuscitation Programme

NWIHP – National Women and Infants Health Programme

PPV – Persistent Pulmonary Ventliation

QI – Quality Initiative

RCTs – Randomised Control Trials

SHO – Senior House Officer

SOL – Spontaneous onset of Labour

TH – Therapeutic Hypothermia

UPI – Uteroplacental ischaemia

Foreword

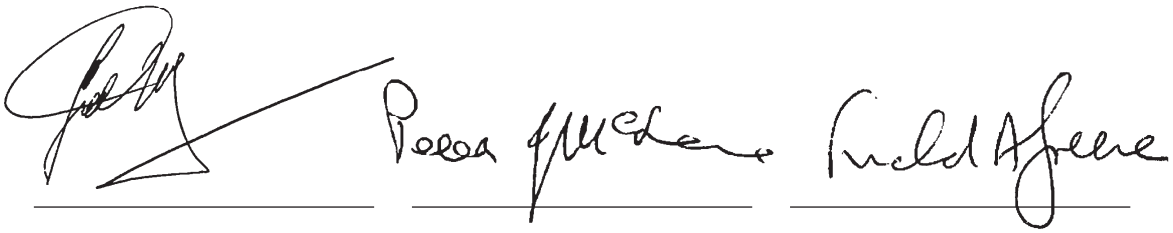
This is the Neonatal Therapeutic Hypothermia report for 2019. The working partnership between the National Perinatal Epidemiology Centre, the National Women and Infant Health Programme and the National Clinical Programme for Paediatrics and Neonatology continues to be productive. This year marks the third published report. The Therapeutic Hypothermia (TH) steering committee continues to oversee the governance of this project and its members remain committed to the building of a national register for TH cases in Republic of Ireland.

The electronic register was launched in early March 2020 and this system was utilised for the 2019 TH data collection. The data was collected and verified by the National TH Co-ordinator who visited the maternity units. The findings are accurate and applicable to clinical practice. This year, for the first time, data was collected on the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) assessment of the infants. This developmental assessment is undertaken when the infant is aged two years. This assessment provides information on the longer-term outcome of the infant cohort.

The National Neonatal Encephalopathy Action Group (NNEAG) which is a collaborative initiative between the National Women and Infants Health Programme (NWIHP), State Claims Agency and Department of Health has been established. The remit of the NNEAG is to reduce avoidable cases of Neonatal Encephalopathy (NE) through the identification of risk factors and the development and implementation of initiatives in the maternity services that will reduce these risks. While acknowledging that many of these adverse outcomes are not preventable, in light of current evidence, the ambition must be to eliminate cases which may be preventable. The Royal College of Obstetrics and Gynaecology 'Each Baby Counts' has set a target to reduce NE by 50%, while it is ambitious this country should have a similar goal.[1]

This year, 2020, has been difficult for the Health Service Executive and its staff due to COVID-19. The impact on the way services are delivered has been challenged. We wish to acknowledge the hard work and unfaltering dedication staffs have shown in the maternity services to ensure both mothers and infants continue to receive high quality care. All maternity sites have again been unwavering in their support for the project and their support enables it to drive forward.

With thanks, we look forward to once again working with all stakeholders in 2021 and building upon the knowledge achieved to date.



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Executive Summary

This Report provides details on the 72 infants in Ireland with Neonatal Encephalopathy (NE) who required Therapeutic Hypothermia (TH) in 2019. Findings on all 281 cases in the four-year period 2016-2019 are also provided. This constitutes a large national cohort recorded for a period during which almost 250,000 infants were born in Ireland. The incidence of TH was 1.2 per 1,000 births in 2019 and the rate of TH for the period 2016-2019 was 1.1 per 1,000 births. The rate year-on-year has remained relatively constant with minor fluctuations suggesting that the underlying factors in its aetiology and causation are consistent and repetitive.

NE is a disorder consisting of abnormal neurological behaviour and seizures present in infants from birth. Most of the cases of NE are due to the lack of oxygen to the infant either before or during labour. It is worth reflecting that up to the late '90s there was no treatment for these infants. Following scientific advances and well conducted Randomized Control Trials (RCTs) a treatment has been available since 2009[2-4]. This treatment is induced Neonatal Therapeutic Hypothermia. Infants undergo total body cooling at 33-34°C for a period of 72 hours, commencing within six hours of birth. TH is now considered the standard of care for infants suffering from moderate and severe NE. All the cases of NE reported in this document received TH.

The purpose of the National Neonatal TH Development Project is twofold. First, it is an analysis of the epidemiology, antecedent obstetric, and intrapartum factors leading to NE. Secondly, it is a documentation of the immediate and subsequent neonatal management and outcome of the infants suffering from NE.

In line with international evidence, this report shows that infants born to first-time mothers are at increased risk of needing TH. Based on data for 2016-2019, the observed risk for these infants was 1.76 per 1,000 births, more than twice the risk of 0.75 per 1,000 observed for infants born to multiparous mothers. In mothers with a BMI >30, the TH rate was 1.5 per 1,000 maternities, compared with 0.9 per 1,000 maternities in those with a BMI <30. Although this finding is amenable to correction, it remains challenging. Mothers from Asian and Black ethnic groups accounted for 10% of the mothers whose infants received TH in 2016-2019. This is twice the 5% that mothers from these ethnic groups accounted for in the female population aged 15-49 in 2016, and so they may be a vulnerable or at risk group. However, the lack of national maternity data on ethnicity limits our ability to assess their risk.

There are two other factors that are noteworthy. First, maternal age does not appear to be associated with the need for TH intervention. Given that most reproductive outcomes are negatively impacted by increasing maternal age, this finding is interesting and reassuring. The second point, is that twins do not feature as a recurrent theme in this cohort of infants.

The finding that twins are not over-represented suggests that once recognised as a risk the obstetric management is satisfactory in this cohort of mothers.

Cardiotocography (CTG) is a tool used by midwives and obstetricians to record the fetal heart rate and contractions and can assist with detecting signs of fetal compromise. This year a blinded review of the intrapartum CTGs from one hour pre-delivery were reviewed by a small panel of experts (for methodology see pg 12). A number of normal control CTGs were also included. Not all infants who required TH in 2019 had ongoing fetal monitoring. As such, 59 of the 72 infants had a CTG available for review by the group. For each case, the CTG for the final 1 hour before delivery was reviewed. The review panel categorised 42 CTGs as pathological, 12 CTGs were categorised as suspicious, and 5 CTGs were deemed to be normal. The subjective nature of CTG interpretation compounds the necessity to ensure a 'second eyes' approach and the need to make clinical decisions based on complete clinical information, particularly progress in labour.

In 2019, 13 mothers had a caesarean section prior to labour. In 12 of these cases, fetal compromise such as placental abruption and decreased fetal movements was identified. Four of the mothers who were classified as never-in-labour had presented themselves to hospital querying that spontaneous onset of labour had commenced. The difficulty in diagnosing labour is an emerging issue and has been noted in other reports[5].

This year, for the first time, the report details times related to the care and labour of mothers with Spontaneous Onset of Labour (SOL) though documented times were unavailable for 1 in 4 mothers. For those with data available, half of the mothers had their labour diagnosed within approximately one hour of admission to hospital. Twenty eight percent of mothers who presented themselves to hospital with a possible diagnosis of SOL, were not admitted to the labour ward for greater than 5 hours. Over the four year period detailed in this aggregate report, only 4 infants of the combined total of 281 infants who required TH were delivered by elective section. This strongly suggests that labour and its management are important determinants of an outcome that requires TH intervention.

In 2019, 26 of the mothers whose infants developed NE requiring TH had their labour induced, 17 of these 26 mothers were nulliparous. Only four of these mothers were noted to have a documented favourable cervix, and in 14 cases the Bishop score was less than six. Senior involvement and continual risk assessment in this cohort of mothers is advocated.

Shoulder dystocia was associated with the delivery of 12.8% of the 281 infants who received TH in 2016-2019. This is 19 times more common than recorded for all mothers who gave birth in hospital during 2016-2019, according to Hospital In-Patient Enquiry data. Compared to the other TH cases, those affected by shoulder dystocia more often involved first-time mothers, mothers who were overweight/obese, had an induction of labour and those with higher birthweight infants.

As noted in previous years, being a small for date's infant is associated with the need for TH intervention. There is an excess number of small-for-dates infants in the TH group (P<0.001). The rate of birthweight <10th centile in the infants who underwent TH in the four year timeframe 2016-2019, is 174 per 1,000 compared with 100 per 1,000 in the general population.

Many infants with NE are severely compromised at birth. It is a condition with a high morbidity and a high mortality. In 2019, 15 of the infants with NE requiring TH died. Over the four years of data collection, there have been 39 deaths representing a 14% mortality rate amongst the cohort. Not all cases of NE are avoidable but some may be. Only through reflective and critical evaluation can we learn how different, but reasonable, clinical management could alter the outcome. This year we are including a suggested template for use when reviewing cases of NE requiring TH (see Appendix A). This template has been designed to reflect the sentinel events and the recurring themes which have emerged in the aggregate NE cases requiring TH over the four years from 2016-2019.

Over the four year period 2016-2019, there was a moderate non-significant preponderance of male infants with NE requiring TH with 158 male infants compared to 123 female infants. The need for intensive neonatal resuscitation in 2019 was frequent, 60% of infants required endotracheal intubation and 35% required cardiac compressions. In 2019, 19% of infants detailed in this report had no heart beat at 1 minute. In 2019, 80% of infants had a very low APGAR score (0-3) at 1 minute. Over the 4 years 2016-2019, 51 infants had no heart rate at birth. All these infants required extensive resuscitation highlighting the importance of having suitably trained personnel with up-to-date neonatal resuscitation programme (NRP) certification at all maternity sites, who are capable of performing neonatal resuscitation. A National Neonatal Resuscitation Programme (NRP) co-ordinator took up post in October 2020. The NRP Co-ordinator will establish the national governance for the provision of NRP training and its implementation.

In 2019, 46 (64%)of infants requiring TH were born in a maternity unit with a tertiary Neonatal Intensive Care Unit (NICU) and the other 26 (36%) of infants were transferred from a peripheral unit to the tertiary centre for on-going neonatal care and assessment. In 2019, all 26 outborn infants were initially passively cooled. In 80% of these cases a referral call was made to the tertiary centre within two hours of the birth. From the outborn group 84% were transferred by the National Neonatal Transport Programme (NNTP), and the other cases by the referring hospital's team. TH was continued during transport in all cases where infants were transferred to a tertiary centre. The vast majority of infants (90%), both inborn and outborn, achieved optimal core temperature 33-34°C within six hours of birth.

In 38 cases a venous blood gas was drawn for the initial infant blood gas, 12 gases were capillary and 20 gases were arterial. Venous blood samples are not the gold standard for infant blood gases especially in cases where a baby is suspected of requiring TH. In cases where an infant is compromised and suspected of requiring TH clinicians should aim to carry out a capillary or arterial blood gas as the first infant gas as both of these samples give more meaningful information with regard to the infants condition.

It is strongly recommended that the decision to institute TH for an infant with suspected NE should be based on the Cooling Candidacy Checklist (see Appendix B). The criteria includes; the history of a sentinel event, low APGAR score, low cord pH, base excess ≥ 16mmol/l, continued need for positive pressure ventilation or intubation beyond 10 minutes, and an abnormal neurological examination. In 2019, the checklist was used in 67% of cases. It is urged that the Cooling Candidacy Checklist is used every time TH is being considered for an infant to help ensure the consistent application of TH treatment.

The Sarnat score is the optimal way of accurately categorising an infant's grade of encephalopathy. The score provides a record of the infant's neurological impairment. The score is also recommended by the updated British Association of Perinatal Medicine (BAPM) guidelines 'Therapeutic Hypothermia for Neonatal Encephalopathy[6]. In 2019, the Sarnat score was performed on 65% of infants on day 1, 42% on day 2, and 40% on day 3 of cooling. As a consequence 31% of cases had no grade of encephalopathy assigned at the time of discharge. Where an assessment was made the grading of encephalopathy was severe (13%), moderate (42%), mild to moderate (7%) or mild (7%). A local Quality Initiative (QI) Project in a tertiary maternity hospital demonstrated an improvement in documented neurological assessment for 2019 TH cases[7]. A national roll-out of this QI is warranted to achieve improvements with regard to documentation of neurological assessments for infants undergoing TH. Teaching score cards have been made available and distributed to the four tertiary sites offering TH (see Appendix C).

The Amplitude Integrated Electroencephalogram (aEEG) is the other important tool in the assessment of the infant's neurological status. Daily documentation should be entered while the infant is undergoing TH[8]. In 2019, the aEEG findings were not recorded in 48%

of cases on day 1, 62% on day 2, and 72% on day 3 of TH. A teaching tool is available on the RCPI website. In 2019, one third of infants had seizures over the first three days of life. This represents a reduction in the seizure burden compared with the pre-cooling era when seizures were very common.

Among the various laboratory investigations undertaken for each infant in 2019, the one to pay attention to is the serum sodium as 65% of the TH infants a serum sodium less than 131mmol/l. Conceivably a low sodium value in this setting reflects a hypoxic brain and kidney injury.

Persistent nasogastric feeding beyond 72 hours and particularly at discharge is indicative of persistent neurological impairment. Almost 30% of infants needed nasogastric feeds beyond 72 hours and 10% were still on tube feeds on day of discharge home.

In all of TH cases in 2019 infants were administered antibiotics. While a blood culture was performed in every case, only 20% subsequently had a lumbar puncture undertaken. A micro-array test was performed in 5% of cases. There should be a standardised approach to these investigations for all infants undergoing cooling.

A brain MRI scan is routinely undertaken in all infants with NE treated with TH. It is an important predictor of both short-term and long-term neurological and developmental outcome. It is generally advised to undertake the scan in the first 5-10 days of life. In the 2019, 90% had an MRI by day 10, and the other 10% had one between days 10-15. For the purposes of this report the infants' MRI scans have been assessed using the Barkovich scoring system. Of the available MRI brain reports from the 4 year period 2016-2019, 114 (40%) were abnormal. The most common abnormality encountered was ischaemic changes in the cerebral cortex. The most severe injuries were those involving the thalamus, lentiform nucleus, and peri-rolandic cortex.

The relationship between NE and placental pathology is complex. TH may rescue infants from some of the consequences of placental disease The current understanding of most clinicians is that pre-existing placental pathology may compromise the fetal ability to withstand the stress of labour, and in some cases may directly cause damage to the fetal brain and other organs. One of the aims of the project is get a better picture about the interaction between placenta pathology and birth asphyxia. Perinatal pathologists point out that the placenta is the 'black box' of the pregnancy. The first challenge that we face is that the placenta is not routinely retained and examined in cases of NE requiring TH. The overall placental histology capture rate in 2019 was 74% and the capture rate of the project from 2016-2019 is 76%. In simplistic terms, placental pathologies take place in the maternal plate, the fetal plate, or the cord. Of the available reports, the more common abnormalities encountered in the 2019 data were cord pathologies (34%), maternal vascular malperfusion (12%), chorioamnionitis (10%) and fetal vascular malperfusion (8%). Multiple pathologies are common and study of patterns of placental damage can help understand fetal compromise.

This year a small number of the results from the BSID-III carried out at 2 years were available. The application of this assessment remains inconsistent nationally and as such, due to the small numbers it is difficult to draw any conclusions and interpret trends and emerging themes at this point. It can be seen from this small cohort that both expressive communication and gross motor development may require special attention when devising developmental guidelines for children who have been diagnosed with NE who have had TH. Funding has been approved and sites are in the process of hiring suitable personnel to perform the BSID-III for TH infants. It is anticipated that accurate and consistent data will be captured once these roles have been filled.

In conclusion there are a number of obstetric and neonatal factors that should receive additional attention;

The obstetric factors that require consideration are;

- The use of a standard fetal growth chart nationally
- An agreed criteria for the standardised management of mothers from time of admission until the diagnosis of labour
- Agreed criteria for the diagnosis of labour
- Documentation of a favourable cervix and Bishop score when undertaking an induction of labour
- Standardised interpretation of the CTG
- Standardised management of shoulder dystocia.

The neonatal factors that require consideration are;

- Cord blood gases in every case
- Serum lactate measurement in every case
- Daily documentation of the Sarnat score during TH
- The aEEG record to include the amplitude, presence or absence of seizures, the presence or absence of sleep/wake cycling during TH
- Brain MRI by day 10 reported with the Barkovich score
- Retention and examination of the placenta in every case of TH.

NE remains a challenging condition. The continued national dataset collection, however, provides an insight into how it can be tackled.

Key Messages

- NE is a significant cause of enduring morbidity and is the main cause of mortality in normally formed infants. The total mortality rate for infants in the TH cohort for the time period 2016-2019 was 14%.

- During the years 2016-2019, 281 NE infants were treated with TH, indicating an incidence rate of 1.1 per 1,000 births. Consistent data collection, analysis, action and shared learning is needed to reduce the national incidence of NE requiring TH intervention.

- Nulliparous mothers, induction of nulliparous mothers, shoulder dystocia, ethnicity and obesity with BMI >30 are risk factors for TH which require particular attention in their clinical management.

- There is a clear association with incidence of shoulder dystocia and the requirement for TH. Shoulder dystocia is more common in parous mothers in the general population of mothers giving birth. However, from 2016-2019, 69% of the shoulder dystocia cases that required cooling occurred in nulliparous mothers.

- The diagnosis of labour can be a challenge. The accurate and consistent application to diagnosing labour is warranted to ensure appropriate level of care and monitoring is provided to mothers and their infants.

- The antenatal detection of intrauterine growth restriction is important. During the four-year period 2016-2019, 17.4% of infants who underwent TH were small for dates (birthweight <10th centile) but not often detected at birth.

- Over the four year period, 40% of TH infants were born in a peripheral hospital and required transfer to one of the four tertiary centres that deliver TH intervention. The NNTP plays an important role in the retrieval of NE infants requiring TH intervention from peripheral hospitals. The data in this report reinforces that the Irish Health Service is providing TH in Ireland by way of continuum of care between referral hospital, NNTP and tertiary centres.

- Good documentation is the platform for improvement in the assessment, categorisation, and management of infants with NE. Accurate clinical measurement is the best pathway to improved outcomes for this group of infants.

- Through the 4 year national data collection on infants with NE, a number of recurring key performance indicators have emerged. In all cases of NE the following data items should be recorded:
  - The cord blood gases, both arterial and venous.
  - First infant blood gas
  - The serum lactate in the first infant gas.
  - The Cooling Candidacy Checklist
  - The SARNAT score
  - The aEEG findings- amplitude, sleep-wake cycling, seizures
  - The brain MRI scan report
  - The categorisation of the grade of encephalopathy at the time of discharge.
  - The placenta macroscopic and microscopic examination
  - The BSID-III report for those infants who are now 2 years old.

Recommendations

1. **Enhanced awareness of the important risk factors for NE (first time mothers, IUGR etc.) through standardisation of care pathways and multi-disciplinary training among front line staff is needed.**
The findings from this report provide additional information to help improve the understanding of the risk factors associated with NE. Improving knowledge through the introduction of training programmes and tools for front line staff to help develop strategies for minimising delays and initiating interventions if appropriate. This enhanced awareness should be an ongoing evaluation particularly in labour and take account of the rapidly changing environment.

2. **A National standardised assessment for the diagnosis of fetal growth restriction (FGR) is warranted and should include multi-disciplinary training.**
International evidence illustrates that suboptimal fetal growth is linked to both short and long-term adverse outcomes. Findings from this report illustrates there was some evidence of poor fetal growth with almost 20% of the infants born below the 10th centile. The establishment of a multidisciplinary working group to address a national standardised approach for the detection of FGR is warranted.

3. **Multi-disciplinary skills and drills training to deal with obstetric sentinel events are required.**
Sentinel events; such as uterine rupture, placental abruption and shoulder dystocia, are acute events that are associated with NE. Training, with 2 yearly re-certifications, on the management of major obstetric situations is required for all health professionals involved in the care of mothers in pregnancy.

4. **Front line staff responsible for CTG interpretation are recommended to undertake annual training.**
Fetal monitoring, including continuous cardiotocography (CTG), requires expert knowledge and interpretation and should be undertaken by skilled front line staff. The standardisation and the consistent application of the interpretation of CTG and subsequent clinical response should be encouraged. The appointment of a National Fetal Monitoring and Obstetric Emergencies coordinator is advocated to provide national governance and training for CTG interpretation and Obstetric Emergency care with 2 yearly re-certification.

5. **Not all cases of TH can be avoided but some could be. A comprehensive review of each case of TH is recommended.**
Distinguishing between unavoidable, potential avoidable and avoidable cases of NE requiring TH is an important component for understanding the aetiology and reducing the frequency of TH cases. All cases of TH should have a robust review carried out locally initially. Appreciating that smaller hospitals may not be involved in the review process very frequently, a template has been developed to assist sites (see appendix A).

6. **Umbilical cord blood gas measurements are required in every case where an infant requires TH.**
The findings from this report have indicated that cord blood gas measurements were not taken in 15% of cases. The cord blood gas measurements are an important part of the assessment in infants with NE requiring TH and should be recorded in each case of NE.

7. **Serum lactate on the cord blood or first Infant blood gas for infants requiring TH.**
The anaerobic metabolism in response to hypoxia and poor tissue perfusion leads to an increase in the production of lactate. Raised serum lactate levels especially over 15 mmol/L can be a marker for adverse outcome. In every case of NE, the serum lactate should be part of the infant's assessment.

8. **The Neonatal Resuscitation Programme (NRP) certification is required for all midwives, nurses, and paediatric doctors working in maternity and neonatal units.**
All midwives and neonatal staff engaged in the delivery and care of newborn infants should have up-to-date instruction and training in neonatal resuscitation. The national NRP co-ordinator took up post in October 2020 to provide governance for the NRP programme within the 19 maternity units.

9. **The Cooling Candidacy Checklist should be used as the decision making tool in the evaluation of the infant for therapeutic hypothermia.**
The Cooling Candidacy Checklist is the tool that should be applied when deciding to commence an infant on TH. The findings of the evaluation should be entered in the infant's case notes. Our findings indicate that it is only being used in 67% of cases. A copy of the checklist is included in this report (Appendix C)

10. **All infants receiving TH require a daily Sarnat assessment during the three days of cooling.**
The Sarnat grading scale is an internationally recognised classification assessment tool for NE in the newborn infant. Daily assessment is necessary to assess the progression of encephalopathy. The 2019 TH report similar to 2016/2017/2018 reports has found incomplete Sarnat assessment.

11. **All infants receiving TH require a daily aEEG report during the three days of cooling.**
The following aEEG parameters should be recorded daily during the period of cooling: Amplitude – Continuity – Sleep/Wake Cycling – Presence of seizures.

An e-learning programme on aEEG interpretation is available on the RCPI web site[8]. An appendix on the interpretation of aEEG is attached (Appendix D).

12. **Brain MRIs should be performed between days 5-10 after birth and the reporting should be standardised using the Barkovich Score.**
Brain MRI is the modality of choice for assessment of brain injury severity in cases of NE. Timing of the MRI scan is important in the identification of the initial diffusion changes. If there is a delay in undertaking the scan the early findings can be missed because of pseudo normalisation. Standardisation of the reports using the Barkovich score is recommended. A copy of the Barkovich scoring system is attached (appendix E).

13. **The retention of the placenta for histopathology examination in all cases where there was documented fetal distress during labour and/or the infant subsequently requires admission to the neonatal unit.**
The findings of this report indicate that placental examination is not being undertaken in 26% of cases requiring TH. Given that a decision to treat an infant with TH does not always occur at birth, it is recommended that the placentas where there was documented fetal distress during labour are retained. With the increasing use of the Amsterdam criteria[9,10] for placental reporting, the potential for exploration of the associations of placental pathology, neonatal course and developmental outcome is enhanced. It is therefore critically important that placental submission rates in TH reach if not exceed the excellent rates of >95% achieved for stillbirth.

14. **BSID-III Neurodevelopmental follow-up.**
All TH infants should be followed up at 2 years of age with a BSID-III of their motor, cognitive, and speech/language development. The aim is to make this evaluation available to all infants who have been treated with TH. Funding has been allocated for 3 new clinical psychology posts to expand this service.

Introduction

The National Clinical Programme for Paediatrics and Neonatology (NCPPN) in collaboration with the National Perinatal Epidemiology Centre (NPEC) and the National Women and Infants Health Programme (NWIHP) presents its successive report on neonatal TH in the Republic of Ireland for 2019. We now have four years 2016/2017/2018/2019 cumulative comprehensive data to determine the current status and outcomes for infants who underwent TH during this time frame.

This report presents the 2019 data alongside the 2016/2017/2018 data for comparative analysis. By laying out the report in this format it is anticipated that patterns and trends will begin to emerge.

The electronic register was utilised in 2020 for TH data collection and will serve as a much needed platform to inform clinicians of identified maternal and infant trends alongside clinical risk factors which will assist in the development of maternal risk profiles leading to a change in their antenatal and delivery management. Furthermore the e-register will facilitate benchmarking of TH in Ireland against international standards and ensure continuous quality improvement. TH is an evolving treatment and by maintaining a constant record of the data on the e-register, the value of the adjunctive therapies during TH treatment can be accurately assessed with measured outcomes.

SECTION 1
Maternal Characteristics
Maternal Antenatal Course
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SECTION 2
Infant Characteristics
Resuscitation
Assessment for Therapeutic Hypothermia
Transfer to Tertiary Centre
Treatment days 1-3
Investigations
Rewarming
Feeding
Discharge diagnosis and Death
Placenta findings
MRI findings
BSID-III

Methods

Purpose of this report

The primary aim of this report is to present an overview and national statistics on Neonatal TH in the Republic of Ireland for the year 2019. TH is administered in four centres only (National Maternity Hospital, Rotunda Hospital, Coombe Women and Infants University Hospital and Cork University Maternity Hospital). All babies born in other local and regional hospitals needing this treatment are transferred to one of these four centres.

The review will examine the clinical details around each case of Neonatal Therapeutic Hypothermia. This will include the mothers' antenatal details, labour and delivery. The infant's resuscitation, neurological assessment, treatment of seizures, the supportive clinical care the examination of the placenta and follow up data if applicable.

Data Collection

Retrospective reviews of inpatient medical records have been used as a gold standard approach when assessing multiple outcomes and rates of adverse events. Therefore, for the purposes of the National Neonatal TH review, medical records were considered the primary source of information. Data were collected on site and/or via MNCMS in the 19 maternity units/hospitals and neonatal intensive care units or special care baby units (NICU/SCBU) in the Republic of Ireland. The NCPPN, NPEC and NWIHP collected data on all cases of neonatal therapeutic hypothermia in 2019 by taking an active case ascertainment approach.

Processing of the data

Data on all infants who received TH were collected on site in the 19 maternity units/hospitals. The data was uploaded to the electronic register to the NPEC and were processed in a pseudonymised format. No hospital identifiers were included in the dataset, which means these data cannot be attributed to a specific hospital or to a specific individual.

Missing data

To ensure accuracy of information, missing or incomplete data were sought from the respective maternity hospitals/units by the TH Co-Ordinator. For analysis purposes, cases with missing data were excluded from calculations. However, the extent of missing data is reported in the results section.

Continuous CTG review

A review of CTGs was undertaken of the 59 infants who had fetal monitoring undertaken in the one-hour period before delivery. During the review process a random sample of 16 infants delivered in 2019 who did not require TH were included for the CTG group to review. The review group consisted of two consultant obstetricians, one national lead midwife, one midwifery manager and one senior obstetric registrar. For the review process, the group were given a short vignette and shown images of the CTG recorded in the one-hour period before delivery. The vignette provided included the following details when available; maternal age, parity, any documented pre-existing medical and or obstetric conditions, augmentation of labour, length of labour and gestation at delivery. The full medical report including the partogram were not made available to the teams for this review process. Once the CTG was shown to the group, they had to document their decision before discussion began. The group were directed to categorise the CTG as; normal, suspicious, pathological or unsure request input from a colleague. Once the initial decision was documented by each group member a discussion then occurred amongst the group to achieve consensus.

Comparison to National Statistics

Comparisons are made with the most recent publications available, including the Central Statistics Office's Vital Statistics Fourth Quarter and Yearly Summary Report as well as from the Healthcare Pricing Office.

Definitions & Terminology

NE is a clinical condition in the term infant defined by abnormal neurological behaviour, with the onset occurring at or shortly after birth.

NE is manifested by an abnormal level of consciousness, with or without the presence of seizures and is often accompanied by difficulty initiating and maintaining respirations, depressed tone and depressed reflexes, poor suck and swallow.

NE incidence is estimated as 3.0 per 1000 live births and for Hypoxic-Ischaemic Encephalopathy (HIE) is 1.5 per 1,000 live births[11]. NE is graded as mild, moderate or severe using the Sarnat grading system.

A subgroup of infants with NE have been exposed to a hypoxic-ischaemic insult in-utero and therefore they are assigned a diagnosis of HIE. In a proportion of these cases, a sentinel event is identified i.e. placental abruption, uterine rupture etc.

Suggested criteria for an intrapartum hypoxic-ischaemic insult12 include:

(i) Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7 and base deficit ≥ 12 mmol/L).

(ii) Early onset of severe or moderate NE in infants ≥ 34/40.

(iii) A sentinel hypoxic event occuring immediately before or during labour e.g. uterine rupture, placental abruption, cord prolapse etc.

(iv) A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent late or persistent variable decelerations on cardiotocography, usually after a hypoxic sentinel event when the pattern was previously normal.

(v) Apgar scores of 0-3 beyond 5 minutes of life.

(vi) Onset of multisystem involvement within 72 hours of birth.

(vii) Early imaging study showing evidence of acute non-focal cerebral abnormality.

(viii) Exclusion of other identifiable aetiologies e.g. trauma, coagulation disorders, infection or genetic disorders.

TH has been found to be protective in those infants presenting with moderate or severe NE by inhibiting various events in this cascade of HIE injury. Major randomized clinical trials[2–4] involving induced neonatal hypothermia have demonstrated a reduction in death and disability[13–15]. These trials have shown improved outcomes for babies with NE if they are cooled within six hours of birth to a targeted core body temperature of between 33°C to 34°C for a duration of 72 hours with rewarming to normothermic temperature occurring over a 6-12 hour period. TH is considered to be the standard of care for infants with moderate-to-severe NE who meet inclusion criteria.

The inclusion criteria for TH are;

- ≥36 weeks completed gestation with a weight ≥ 1800grams.
- Acidosis (pH<7.0) present in the umbilical cord, or any blood sample taken within 60 minutes of birth.
- Base deficit ≥ -16.0 mmol/L in umbilical cord or any blood sample taken within 60 minutes of birth.
- History of acute perinatal event (such as but not limited to cord prolapse, placental abruption or uterine rupture).
- Apgar score ≤5 at 10 minutes or at least 10 minutes of positive-pressure ventilation.
- Evidence of moderate-to-severe encephalopathy, demonstrated by the presence of seizures OR at least one sign in three or more of the six categories shown In the Modified Sarnat Table (see Table 35[7]).

Main Findings

The following analysis is based on 72 infants who underwent neonatal TH treatment in 2019.

Maternal Characteristics

Age

The age of mothers whose infants underwent therapeutic hypothermia was known for all 72 of the mothers in 2019. The mothers whose infants underwent therapeutic hypothermia ranged in age from teenage years (the youngest being 18 years of age) through to mid-forties (the eldest being 44 years of age). Their age distribution reflected that of the population of mothers who gave birth in Ireland (Table 1). Two thirds of the population (65.6%)[16] who gave birth between 2016 and 2019 were aged 30-39 years. As outlined in Table 2 there was no statistical difference in the risk of TH by maternal age. There were slight variations observed, with slightly higher risk among births to mothers aged under 25 years and lower risk for births to older mothers.

Table 1: Age distribution of mothers whose infants underwent therapeutic hypothermia in 2016-2019 versus all births in 2016-2019

Age group	TH cases N=63 2016	TH cases N=77 2017	TH cases N=68 2018*	TH cases N=72 2019	TH cases N=280 2016-2019	All births[16] N=246,483 2016-2019 (%)
<20yrs	1(1.6)	0(0.0)	3(4.4)	1(1.4)	5(1.7)	1.6
20-24yrs	8(12.7)	8(10.4)	7(10.3)	2(2.8)	25(8.3)	8.2
25-29yrs	9(14.3)	15(19.5)	10(14.7)	16(22.2)	50(17.9)	17.4
30-34yrs	23(36.5)	24(31.2)	25(36.8)	30(41.7)	102(36.4)	34.9
35-39yrs	18(28.6)	25(32.5)	18(26.5)	18(25.0)	79(28.2)	30.7
≥40yrs	4(6.3)	5(6.5)	5(7.4)	5(6.9)	19(6.8)	7.3

Note: Values are shown as N(%) unless otherwise stated. *Age unknown for one mother.
Population data from the Central Statistics Office[19]

Table 2: Risk ratios for infants who underwent therapeutic hypothermia in 2016-2019 by maternal age

Age group	TH cases N=280 2016-2019	Rate (95% CI)	Rate ratio (95% CI)	P-value
<20yrs	5(1.7)	1.26 (0.41-2.95)	1.21 (0.49-2.99)	0.679
20-24yrs	25(8.3)	1.24 (0.80-1.83)	1.19 (0.76-1.87)	0.449
25-29yrs	50(17.9)	1.17 (0.87-1.54)	1.12 (0.79-1.60)	0.531
30-34yrs	102(36.4)	1.19 (0.97-1.44)	1.14 (0.85-1.52)	0.394
35-39yrs	79(28.2)	1.04 (0.83-1.30)	1.00 (ref.)	
≥40yrs	19(6.8)	1.06 (0.64-1.66)	1.02 (0.62-1.68)	0.948

Note: Values are shown as N(%) unless otherwise stated. *Age unknown for one mother. CSO data for births

Ethnicity

Assessment of risk associated with ethnic group is impeded by the absence of national data on ethnicity for the pregnant population in Ireland. The majority of mothers whose infants underwent therapeutic hypothermia in 2019 were of white Irish ethnicity (70.8%, n=51) (Table 3). This is similar to the proportion of white Irish women in the female population aged 15-49 years, enumerated by the National Census 2016. While the numbers involved were small, Irish Traveller, Asian and Black ethnicities were overrepresented in the mothers whose infants underwent therapeutic hypothermia in 2019 (16.7%) compared to 5.3% of the female 15-49-year-old population in the Irish Traveller, Asian and Black ethnicities from the National Census in 2016.

Table 3: Ethnicity of mothers whose infants underwent therapeutic hypothermia in 2016-2019 versus 15-49 year-old female population, 2016

Ethnicity	TH cases N=63 2016	TH cases N=75 2017*	TH cases N=68 2018**	TH cases N=72 2019	TH cases N=278 2016-2019	15-49 year-old female population, 2016***[17] (%)
White Irish	53(84.1)	52(69.3)	49(72.1)	51(70.8)	205(73.7)	79.2
Irish Traveller	0(0.0)	2(2.7)	1(1.5)	1(1.4)	4(1.4)	0.7
Other white background	6(9.5)	14(18.7)	12(17.6)	7(9.7)	39(14.0)	13.7
Asian/Asian Irish	4(6.3)	3(4.0)	2(2.9)	4(5.6)	13(4.7)	2.9
Black/Black Irish	0(0.0)	4(5.3)	3(4.4)	7(9.7)	14(5.0)	1.7
Other/mixed	0(0.0)	0(0.0)	1(1.5)	2(2.8)	3(1.1)	1.9

Note: Values are shown as N(%) unless otherwise stated. *Ethnicity unknown for two mothers.
**Ethnicity unknown for one mother. ***Population data from the National Census 2016[17]

Employment and insurance status

Table 4 provides a high-level overview of the data provided on mother's employment status, alongside data available for the most comparable occupation categories for mothers of all births in Ireland[17] and for the 15-44 year-old female population from the National Census 2016. Employment status was specified for all of the mothers for whom data were recorded in 2019 (100%; n=72). It can be seen that unemployed status was recorded for 5.8% of the mothers whose infants underwent therapeutic hypothermia compared to 4.5% of all mothers in 2016 and 8.2% of the female population aged 15-44 years (Table 4). The proportion of mothers engaged in home duties whose infants underwent therapeutic hypothermia (15.3%) was lower than the percentage of all women engaged in home duties who gave birth in 2016 (20.5%).

Health insurance status was recorded for the 72 mothers whose infants underwent therapeutic hypothermia in 2019 and for 65 of the 69 mothers whose infants underwent therapeutic hypothermia in 2018. In total, 90% of these mothers were public patients (n=123 of 137, 89.8%) while 10% attended a consultant obstetrician privately (n=14, 10.2%). This shows an over-representation of public patients among mothers whose infants underwent therapeutic hypothermia as, according to HIPE data, 82.0% and 18.0% of all mothers who gave birth in hospital in 2018-2019 were public and private patients, respectively. The risk of TH for the infants of public patients was 1.28 (95% CI=1.06-1.52) per 1,000 women, which was almost twice the risk of 0.66 (95% CI=0.36-1.11) per 1,000 women among private patients (Risk ratio=1.93, 95%=1.11-3.36, p-value=0.020).

Table 4: Employment status at booking of mothers whose infants underwent therapeutic hypothermia in 2016-2019 versus all births in 2016 and 15-44 year-old female population in 2016

Occupation	TH cases N=53 2016*	TH cases N=65 2017**	TH cases N=66 2018***	TH cases N=72 2019	TH cases N=256 2016-2019	All maternities 2016 (%)	15-44 year-old female population, 2016+ (%)
Employed	43(81.1)	48(73.8)	49(74.2)	53(73.6)	193(75.4)	73.1	57.8
Unemployed	1(1.9)	10(13.0)	11(16.7)	4(5.8)	26(10.2)	4.5	8.2
Home duties	5(1.9)	4(5.2)	3(4.5)	11(15.3)	23(9.0)	20.5	10.4
Student	4(7.5)	3(3.9)	3(4.5)	3(4.2)	13(5.1)	n/a	21.1
Others not in labour force	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1(0.4)	n/a	2.5

Note: *Data not known on employment for 10 mothers. **Data not known on employment for 12 mothers.
***Data not known on employment for 2 mothers. +Population data from the National Census 2016[17]

Body Mass Index

Body Mass Index (BMI) was available for 69 of the 72 mothers whose infants underwent therapeutic hypothermia in 2019 (Table 5). The pattern of BMI in the mothers was similar to that from the general population who participated in the 2019 Healthy Ireland Survey[18]. The BMI of 31.9% of these mothers was in the obese range (>30.0kgm^{-2}), which is higher than those from the general population.

Table 5: Body mass index of mothers whose infants underwent therapeutic hypothermia in 2016-2019 versus body mass index of mothers in the Healthy Ireland Survey in 2019

BMI Category (kg/m^2)	TH cases N=62 2016*	TH cases N=72 2017**	TH cases N=62 2018**	TH cases N=69 2019***	TH cases N=262 2016-2019	Healthy Ireland Survey 2019 (%)[18]
Underweight (<18.5)	1(1.6)	2(2.8)	0(0.0)	0(0)	3(1.1)	1
Healthy (18.5-24.9)	22(35.5)	33(45.8)	23(37.1)	30(43.5)	108(41.2)	44
Overweight (25.0-29.9)	22(35.5)	20(27.8)	19(30.6)	17(24.6)	78(29.8)	33
Obese (>30.0)	17(27.4)	17(23.6)	20(32.3)	22(31.9)	73(27.9)	22

Note: Values are shown as N(%) unless otherwise stated. *BMI value missing for six mothers.
**BMI value missing for five mothers. ***BMI value missing for three mothers.

Smoking and substance abuse

Of the 72 mothers whose infants underwent therapeutic hypothermia in 2019, nine mothers (12.5%) were smokers at the time of booking; this is slightly lower than the prevalence of all female smokers in the Irish population in 2018 (17%)[11]. Information on smoking was available for seven of the nine smokers (77.8%). Four mothers were smoking between 1 and 5 cigarettes per day (n=4 of 7, 57.1%) and three were smoking between 11 and 20 cigarettes per day (n=3 of 7, 42.9%). Of the seven mothers who were smoking at booking, none of the mothers stopped smoking during pregnancy. There were no pregnancies with a documented history of alcohol abuse, but one woman had a documented history of drug abuse who used cannabis during pregnancy.

Previous pregnancy

In terms of parity of mothers who delivered infants requiring TH in 2019, there was an overrepresentation of mothers who had not previously delivered (59.7%) compared to the general population of mothers who gave birth in 2016 (38.2%; Table 6). Table 7 outlines the risk of TH among infants born to multiparous mothers, with little variation between the numbers of previous deliveries.

Considering all infants born to multiparous mothers as one group, there were 115 cases of TH in 2016-2019 and their risk of TH was 0.75 (95% CI=0.62-0.91) per 1,000 births. Compared to these infants, the risk of TH was 2.34 times higher among those born to nulliparous mothers (Risk ratio=2.34, 95% CI=1.84-2.97, p-value<0.001).

Table 6: Distribution of parity, 2016-2019

Parity	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=72 2019	TH cases N=281 2016-2019	All births* 2016-2019 (%)
Nulliparous	42(66.7)	42(54.5)	39(56.5)	43(59.7)	166(59.1)	38.2
Para 1	13(20.6)	21(27.3)	19(27.5)	14(19.4)	67(23.8)	34.9
Para 2	5(7.9)	8(10.4)	7(10.1)	8(11.1)	28(10.0)	17.8
Para 3+	3(4.8)	6(7.8)	4(5.8)	7(9.7)	20(7.1)	9.1

Note: Values are shown as N(%) unless otherwise stated. **Population data from the Central Statistics Office[19]

Table 7: Risk ratios for infants who underwent therapeutic hypothermia in 2016-2019 by parity

Parity	TH cases N=281 2016-2019	Rate (95% CI)	Rate ratio (95% CI)	P-value
Nulliparous	166(59.1)	1.76 (1.51-2.05)	2.77 (1.85-4.13)	<0.001
Para 1	67(23.8)	0.78 (0.60-0.99)	1.22 (0.78-1.90)	0.378
Para 2	28(10.0)	0.64 (0.42-0.92)	1.00 (ref.)	
Para 3+	20(7.1)	0.90 (0.55-1.38)	1.40 (0.79-2.49)	0.246

In 2019, 40 mothers had a previous pregnancy. Of these, 33.3% (n=13 of 39; undocumented for one) had a previous pregnancy-related problem reported. As outlined in Table 8, mothers who had experienced three or more miscarriages and having an infant who previously required intensive care were both the most common pregnancy-related problem in mothers who had a previous pregnancy (10%; n=4). None of the mothers had an infant with HIE in a previous pregnancy.

Table 8: Previous pregnancy-related problems in mothers whose infants underwent therapeutic hypothermia in 2019

	TH cases N=28 2016	TH cases N=47 2017	TH cases N=30 2018	TH cases N=40 2019	TH cases N=145 2016-2019*
Previous caesarean delivery	6(21.4)	8(17.0)	6(20.0)	3(7.5)	23(15.9)
Three or more miscarriages	1(3.6)	4(8.5)	1(3.3)	4(10.0)	10(6.9)
Infant requiring intensive care	0(0.0)	3(6.4)	2(6.7)	4(10.0)	9(6.2)
Pre-term birth or mid-trimester loss	2(7.1)	1(2.1)	0(0.0)	1(2.5)	4(2.8)
Neonatal death	1(3.6)	0(0.0)	1(3.3)	0(0.0)	2(1.4)
Pre-eclampsia	2(7.1)	0(0.0)	0(0.0)	1(2.5)	3(2.1)
Stillbirth	1(3.6)	1(3.6)	1(3.3)	0(0.0)	3(2.1)
Placenta abruption	0(0.0)	1(2.1)	2(6.7)	0(0.0)	3(2.1)
Post-partum haemorrhage requiring transfusion	0(0.0)	0(0.0)	1(3.3)	0(0.0)	1(0.7)
Infant with congenital anomaly	0(0.0)	0(0.0)	(0.0)	1(2.5)	1(0.7)
Other	0(0.0)	1(2.1)	2(6.7)	3(7.5)	6(4.1)
Placenta praevia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Previous infant with HIE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: *Percentage relates to total number of mothers who had a previous pregnancy (n=145). Categories are not mutually exclusive. Values are shown as N(%) unless otherwise stated

Pre-existing medical problems

Almost half of the mothers, whose infants underwent TH in 2019, had one or more pre-existing medical problems (n=35, 48.6%). Twenty-one of the 72 mothers were taking prescribed medication during the pregnancy (29.2%). Six mothers had a documented family history of conditions which can affect newborn infants (8.3%; n=6). The most common type of pre-existing medical problems were endocrine disorders, with 18.1% of mothers (n=13) suffering from conditions of this type (Table 9). Psychiatric disorders had the second highest percentage of occurrence (6.9%, n=5).

Table 9: Pre-existing medical problems in mothers whose infants underwent therapeutic hypothermia in 2019

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=72 2019	TH cases N=281 2016-2019
Endocrine disorder	7(11.1)	3(3.9)	6(8.7)	13(18.1)	29(10.3)
Psychiatric disorder	4(6.3)	3(3.9)	6(8.7)	5(6.9)	18(6.4)
Hypertension	3(4.8)	1(1.3)	0(0.0)	1(1.4)	5(1.8)
Haematological disorder	1(1.6)	2(2.6)	0(0.0)	0(0.0)	3(1.1)
Diabetes	1(1.6)	1(1.3)	1(1.4)	0(0.0)	3(1.1)
Cardiac disease	0(0.0)	1(1.3)	1(1.4)	3(4.2)	5(1.8)
Inflammatory disorder	0(0.0)	1(1.3)	0(0.0)	0(0.0)	1(0.3)
Renal disease	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Epilepsy	0(0.0)	(0.0)	2(2.9)	2(2.8)	4(1.4)
Other	7(11.1)	18(23.4)	9(13.0)	17(23.6)	51(18.1)

Note: Percentage relates to total number of mothers, categories are not mutually exclusive

Antenatal care

Currently in Ireland, there is no national data on the number of births as a result of fertility treatment. Information was available for all of the mothers whose infants underwent therapeutic hypothermia in 2019. In five of these cases (6.9%), the pregnancy was reported to be the result of fertility treatment. In vitro fertilisation was the method of fertility treatment specified for three of the five pregnancies and over half of these mothers were aged 40 years or older (60.0%; n=3 of 5). In terms of parity the majority of mothers were nulliparous (80.0%; n=4 of 5).

During this pregnancy, the majority of the 72 mothers intended on delivering in an obstetric unit (95.8%; n=69) with obstetric-led care (88.9%; n=64). Gestation at booking was unknown for one woman and no mothers were unbooked in 2019 (Table 10). A third of mothers had their first antenatal appointment before 12 weeks gestation (36.1%; n=26) and over half of the mothers between 12 and 15 weeks gestation (55.6%; n=40). Estimated Date of Delivery (EDD) was documented for all 72 of the mothers. EDD was confirmed using ultrasound scan in the majority of cases (95.8%; 69 of 72).

Table 10: Timing of antenatal hospital booking appointment for mothers whose infants underwent therapeutic hypothermia in 2016-2019

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=72 2019	TH cases N=281 2016-2019
Less than 12 weeks	16(25.4)	22(28.6)	14(20.3)	26(36.1)	78(27.8)
12-15 weeks	40(63.5)	40(51.9)	40(58.0)	40(55.6)	160(56.9)
15-19 weeks	5(7.9)	9(11.7)	7(10.1)	3(4.2)	24(8.5)
20 weeks of later	2(3.2)	2(2.6)	1(1.6)	2(2.8)	7(2.5)
Unknown	0(0.0)	4(5.2)	5(7.2)	1(1.4)	10(3.6)
Unbooked	0(0.0)	0(0.0)	2(2.9)	0(0.0)	2(0.7)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for one mother

Gestation at last antenatal hospital visit

Information on the last antenatal visit was available for 69 of the 72 mothers whose infants underwent TH in 2019 (95.8%). These 69 mothers last attended the hospital clinic between 28 and 41 weeks. The majority of mothers attended at 37 weeks or later (88.4%, n=61 of 69) with 17.4% (n=12 of 69) last attending the hospital before the last routine antenatal clinic visit at 37 weeks gestation (Figure 1). Two of these 12 mothers (16.7%) were reported to have missed antenatal appointments as they did not attend on multiple occasions. Of the 72 mothers, one mother was transferred from another maternity unit with the fetus in utero at 22 gestational weeks.

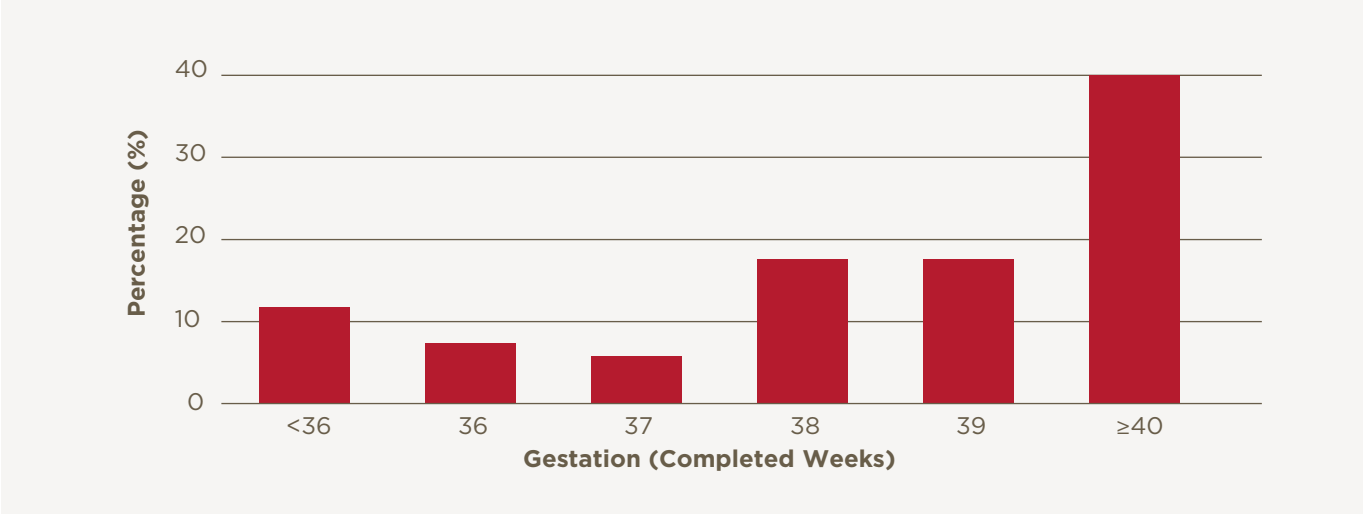


Figure 1: Weeks gestation at last antenatal visit, 2019

Concern documented during pregnancy

Of the 72 cases, there were concerns documented during the pregnancy for 28 (38.9%) of the mothers whose infants underwent therapeutic hypothermia in 2019. Three of these mothers had two or more concerns documented (17.9%; n=5 of 28). The most common concern documented was gestational diabetes mellitus with 11.1% (n=8 of 72) of mothers developing this condition during pregnancy. This was followed by suspected intrauterine growth restriction and hypertensive disorders which both had the second highest percentage of occurrence (6.9%, n=5 of 72 respectively). Concern over non-attendance at antenatal appointments was the fourth most common concern documented for these pregnancies (4.2%; n=3 of 72).

Labour

Information on the onset of labour was available for all 72 mothers whose infants underwent TH in 2019 (Table 11). Almost half of the mothers laboured spontaneously (45.8%; n=33), over a third of mothers were induced (36.1%; n=26) and 18.1% of mothers were never in labour.

Table 11: Onset of labour for mothers whose infants underwent therapeutic hypothermia in 2016-2019

	Total	Nulliparous				Parous			
	N=281	2016 N=42	2017 N=42	2018 N=39	2019 N=43	2016 N=21	2017 N=35	2018 N=30	2019 N=29
Spontaneous	135(48.0)	19(45.2)	22(52.4)	19(48.7)	17(39.5)	10(47.6)	18(51.4)	14(46.7)	16(55.2)
Induction	97(34.5)	22(52.4)	13(31.0)	12(30.8)	17(39.5)	6(28.6)	7(20.0)	11(36.7)	9(31.0)
Never in labour	49(17.4)	1(2.4)	7(16.7)	8(20.5)	9(20.9)	5(23.8)	10(28.6)	5(16.7)	4(13.8)

Note: Values are shown as N(%) unless otherwise stated

As outlined in Table 12, over half of mothers who laboured spontaneously presented to the emergency department (51.5%, n=17 of 33). Of these mothers, the majority presented with either spontaneous rupture of membranes (n=8 of 33) or spontaneous onset of labour (n=15 of 33).

Of the 26 mother who were induced, 23 of those were planned inductions (88.5%; n=23 of 26) with the majority of mothers presenting to the antenatal ward for admission for delivery (84.6%; n=22 of 26).

Table 12: The department that mothers attended when presenting to the hospital for admission for queried onset of spontaneous labour 2019

TH cases 2019	Total N=72	Spontaneous N=33	Induced N=26	Never in labour N=13
Maternity Emergency Department	28(39.9)	17(51.5)	2(7.7)	9(69.2)
Antenatal Wards	29(40.3)	5(15.2)	22(84.6)	2(15.4)
Labour Wards	10(13.9)	7(21.2)	2(7.7)	1(7.7)
Other	5(6.9)	4(12.1)	0(0.0)	1(7.7)

Note: Values are shown as N(%) unless otherwise stated.

For the first time in 2019, documented times were sought relating to when the mother was admitted to hospital, diagnosed as being in labour, admitted to the labour ward, when she began to push and when the baby was born. Twenty-five of the 33 mothers with spontaneous onset of labour had data available for most of these stages. Half of the 25 mothers had their labour diagnosed within approximately one hour of their admission to hospital (n=13, 52.0%), 5 mothers (20.0%) had their labour diagnosed approximately two hours after hospital admission and for the other 7 mothers (28.0%) labour diagnosis was made 5-22 hours after admission to hospital.

The mean time from labour diagnosis to labour ward admission was 47 minutes (Table 13; data available for 18 of the 20 mothers). On average, time from labour diagnosis to labour ward admission was longer for nulliparous mothers. The mean time from labour ward admission to starting to push was almost four hours. The mean time was twice as long for nulliparous mothers, at approximately five hours versus two and a half hours for parous mothers. Time from starting to push until delivery of the baby was 33 minutes, on average. Again, this varied by parity, with a mean of 53 minutes for nulliparous mothers and 15 minutes for parous mothers.

Table 13: Mean time of stages of labour for mothers with spontaneous onset of labour in 2019

Stage	n	All	Nulliparous	Parous
From labour diagnosis to labour ward admission	18	00:47	01:12	00:21
From labour ward admission to starting to push	18	03:45	04:53	02:37
From starting to push to delivery of the baby	21	00:33	00:53	00:15

Note: n represents the number of mothers with data available. Time values are in the format hh:mm.

Half of the mothers who laboured spontaneously had their labour accelerated (50.0%; n=16 of 32, missing data for one mother), either by artificial rupture of membranes (ARM; 56.3%, n=9 of 16) or oxytocin (31.3%; n=5 of 16). Two mothers (12.5%; n=2 of 16) had their labour accelerated with both (Table 14).

Table 14: Method of acceleration for mothers who laboured spontaneously by parity in 2016-2019

	Total	Nulliparous				Parous			
	N=61	2016 N=11	2017 N=11	2018 N=9	2019 N=10	2016 N=3	2017 N=5	2018 N=6	2019 N=6
ARM	34	3(27.3)	6(54.5	4(44.4)	4(40.0)	3(100)	5(100)	4(66.7)	5(83.3)
Oxytocin	22	8(72.7)	5(45.5)	2(22.2)	4(40.0)	0(0.0)	0(0.0)	2(33.3)	1(16.7)
Both	5	0(0.0)	0(0.0)	3(33.3)	2(20.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: Values are shown as N(%) unless otherwise stated

As outlined in Table 15, liquor was clear in 37 of the 56 documented cases (66.1%). One in every four mothers had meconium-stained liquor (28.6%; n=16 of 56). The grade of meconium was specified for 15 of the 16 cases (93.8%), with 46.7% of these mothers having Grade 1 (n=7 of 15), 26.7% of mothers having Grade 2 (n=4 of 15) and the remaining four mothers having Grade 3 (26.7%).

Table 15: Liquor colour by parity in 2016-2019

	Total	Nulliparous				Parous			
	N=281	2016 N=42	2017 N=42	2018 N=39	2019 N=43	2016 N=21	2017 N=35	2018 N=30	2019 N=29
Clear	132(47.0)	22(52.4)	19(45.2)	16(41.0)	25(58.1)	11(52.4)	16(45.7)	11(36.7)	12(41.4)
Meconium	71(25.3)	11(26.2)	10(23.8)	14(35.9)	7(16.3)	2(9.5)	8(22.9)	10(33.3)	9(31.0)
Other	23(8.3)	5(11.9)	5(11.9)	4(10.3)	2(4.7)	0(0.0)	2(5.7)	4(13.3)	1(3.4)
Missing/ Non-applicable	55(19.6)	4(9.5)	8(19.0)	5(12.8)	9(20.9)	8(38.1)	9(25.7)	5(16.7)	7(24.1)

Note: Values are shown as N(%) unless otherwise stated

Induction

There was a documented reason for induction for 22 of the 26 mothers whose onset of labour was induced (84.6%). As indicated in Table 16, the common reasons to induce labour were associated with post maturity (40.9%%; n=9 of 22), hypertensive disorders (13.6%; n=3 of 22) and large for gestational age (9.1%; n=2 of 22). Under the "Other" category a range of indications were captured including; gestational diabetes mellitus and previous pregnancy complications.

Table 16: Reason for induction of mothers whose infants underwent therapeutic hypothermia in 2019

TH cases 2019	Total N=22*	Nulliparous N=16*	Parous N=6*
Post maturity	9(40.9)	9(56.3)	0(0.0)
Hypertensive disorders	3(13.6)	2(12.5)	1(16.7)
Large for gestational age	2(9.1)	1(6.3)	1(16.7)
Oligohydramnios	1(4.5)	0(0.0)	1(16.7)
Polyhydramnios	1(4.5)	0(0.0)	1(16.7)
Intra-uterine growth restriction	1(4.5)	1(6.3)	0(0.0)
Prolonged SROM	1(4.5)	1(6.3)	0(0.0)
Reduced fetal movements	1(4.5)	1(6.3)	0(0.0)
Other	6(27.3)	3(18.8)	3(50.0)

Note: Values are shown as N(%) unless otherwise stated. *Categories are not mutually exclusive

It was documented that all 26 mothers who were induced had a cervical assessment carried out (100%, Table 17). The result of the assessment was undocumented in over a quarter of cases (26.9%; n=7 of 26). Almost one quarter of mothers had a favourable result (23.1%; 6 of 26) with similar rates observed for nulliparous and parous mothers (23.5%; n=4 of 17 versus 22.2%; n=2 of 9 respectively). The Bishop score was used for 21 of the 26 mothers who were induced (80.8%). Of these 21 mothers, the median Bishop score was 2 and these scores ranged from 1 to 8.

Table 17: Results of the cervical assessment carried out on mothers who were induced whose infants underwent therapeutic hypothermia in 2019

TH cases 2019	Total N=26	Nulliparous N=17	Parous N=9
Assessment			
Favourable	6(23.1)	4(23.5)	2(22.2)
Not favourable	3(11.5)	2(11.8)	1(11.1)
Neither	10(38.5)	8(47.1)	2(22.2)
Not documented	7(26.9)	3(17.6)	4(44.4)
Bishop Score	**N=21**	**N=14**	**N=7**
0-6	20(95.2)	14(100)	6(85.7)
7-10	1(4.8)	0(0.0)	1(14.3)

Note: Values are shown as N(%) unless otherwise stated

The method of induction was known for all 26 mothers who were induced in 2019 (100%). Two thirds of mothers had their labour induced using multiple methods of induction (65.4%; 17 of 26). As illustrated in Table 18, two thirds of mothers had their labour induced with the artificial rupture of membranes (65.4%; n=17 of 26). The second most common method of induction was the use of prostaglandin gel (61.5%; n=16 of 26) followed by oxytocin (46.2%; n=12 of 26).

Table 18: Method of induction for mothers whose infants underwent therapeutic hypothermia in 2016-2019

	Total	Nulliparous				Parous			
	N=97	2016 N=22	2017 N=13	2018 N=12	2019 N=17	2016 N=6	2017 N=7	2018 N=11	2019 N=9
Oxytocin	55(56.7)	14(63.6)	9(69.2)	7(58.3)	8(47.1)	2(33.3)	4(57.1)	7(63.6)	4(44.4)
Artificial rupture of membranes	54(55.7)	11(50.0)	8(61.5)	6(50.0)	11(64.7)	4(66.7)	4(57.1)	4(36.4)	6(66.7)
Prostaglandin gel	52(53.6)	12(54.5)	6(46.2)	7(58.3)	12(70.6)	4(66.7)	2(28.6)	5(45.5)	4(44.4)
Propress	24(24.7)	6(27.3)	6(46.2)	4(33.3)	4(23.5)	0(0.0)	1(14.3)	1(9.1)	2(22.2)
Other	1(1.0)	1(4.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive.

Never in labour

In 2019, there was a similar proportion of nulliparous mothers (20.9%; n=9 out of 43) who were never in labour compared to parous mothers (13.8%; n=4 of 29) which was lower than the previous years (Table 11). The figures for 2016-2018 reported that 13.0% of nulliparous mothers (n=16 of 123) and 23.3% of parous mothers (n=20 of 86) whose infants underwent TH were never in labour. Of the 13 mothers who were never in labour in 2019, two mothers had previously had a caesarean section (15.4%; n=2 of 13), which is consistent with the mothers from 2016-2018 (14.9% n=7 of 47). Half of the mothers who were never in labour in 2019 had a reported medical problem during this pregnancy (46.2%; n=6 of 13) which included endocrine disorder, psychiatric disorder, hypertension, asthma, sexually transmitted infection and arthrogryposis. The indication for admission to the hospital was recorded for all 13 mothers.

One quarter of mothers who were never in labour were admitted complaining of reduced fetal movements (23.1%; n=3 of 13) and a further one quarter of woman were admitted with a query of spontaneous labour (30.1%; n=4 of 13). The indication for caesarean section was recorded for all 13 mothers, with half due to a non-reassuring CTG in 2019 (53.8%, n=7 of 13) which is lower than the 74.5% (n=37 of 47) of mothers between 2016 and 2018. One-quarter of mothers were brought to theatre for caesarean section in 2019 due to placental abruption (23.1%, n=3 of 13) compared to 8.5% (n=4 of 47) between 2016 and 2018. Of the remaining three mothers in 2019, the indication for caesarean section included antepartum haemorrhage, eclamptic seizures and one woman with a planned caesarean section.

Fetal heart monitoring

Fetal heart monitoring was undertaken for 68 of the 72 mothers whose infants underwent TH in 2019 (94.4%). The method of fetal heart monitoring was documented for all 68 mothers (100%). As illustrated in Table 19, external continuous fetal heart monitoring was the most common method of monitoring used during labour (91.2%; n=62 of 68). Seven mothers who underwent external continuous fetal heart monitoring also had internal continuous fetal heart monitoring (11.3%; n=7 of 62). Two thirds of all mothers who had fetal monitoring undertaken had external intermittent fetal heart monitoring (63.2%; n=43 of 68). Of these mothers, the majority also underwent external continuous fetal heart monitoring during labour (86.0%; n=37 of 43).

Table 19: Method of fetal heart monitoring for infants who underwent therapeutic hypothermia in 2016-2019

	Total	Nulliparous				Parous			
	N=239	2016 N=40	2017 N=34	2018 N=37	2019 N=42	2016 N=13	2017 N=23	2018 N=24	2019 N=26
External continuous	205(85.8)	36(90.0)	26(76.5)	36(97.3)	37(88.1)	9(69.2)	15(65.2)	21(87.5)	25(96.2)
External intermittent	105(43.9)	16(40.0)	10(29.4)	11(29.7)	28(66.7)	5(38.5)	9(39.1)	11(45.8)	15(57.7)
Internal continuous	23(9.6)	1(2.5)	2(5.9)	6(16.2)	4(9.5)	0(0.0)	1(4.3)	6(25.0)	3(11.5)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

Data on cardiotocography (CTG), which could be interpreted, were available for 59 of the 62 cases (93.7%) who had external continuous fetal heart monitoring. Of these 59, one in five were interpreted as suspicious (20.3%; n=12 of 59) and almost three quarters were interpreted as pathological (71.2%; n=42 of 59). One fetal blood sample was taken for four of the 72 infants who underwent TH in 2019 (5.6%). One in four of the fetal blood samples was categorised as abnormal (25.0%; n=1 of 4).

Delivery

Information on both the day and time of birth was available for all 72 infants who underwent TH in 2019. The timing of birth was categorised between 08:00 and 19:59 hours and 20:00 and 07:59hrs. As illustrated in Figure 2, the time of birth varied across the seven days of the week. One third of infants who underwent TH in 2019 were born at the weekend or on a bank holiday (33.3%; n=24). Of all of these births, two thirds were born between 20:00 and 07:59 hours (65.3%; n=47).

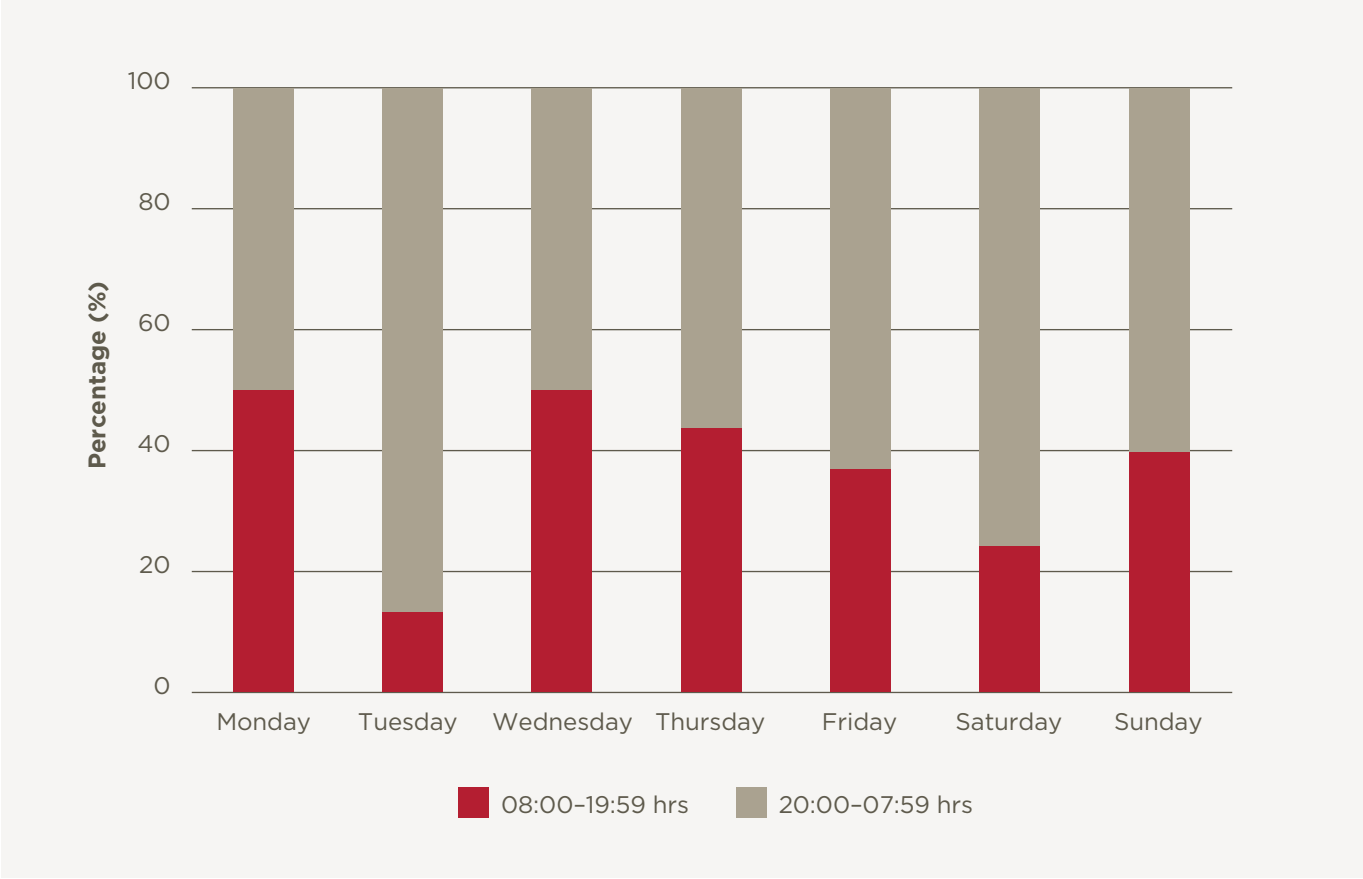


Figure 2: Day of week and time of birth (08:00 – 19:59 and 20:00 – 07:59) for infants who underwent therapeutic hypothermia in 2019

The type of care received at delivery was known for all mothers whose infants underwent TH (n=72). The vast majority of the infants (97.2%; n=70) were delivered under obstetric-led care, which is the predominant model of care in Ireland. Two infants were born before arrival at the maternity unit.

Presentation at delivery was known for 96.6% of mothers who laboured before delivery (n=57 of 59). The majority of presentations at delivery were vertex presentations (n=52 of 57, 91.2%), and in three cases the presentation was breech (n=3 of 57, 5.3%).

Mode of delivery was known for all mothers (n=72) whose infants underwent TH in 2019 (Table 20). One in five of infants had a spontaneous vaginal delivery (33.4%, n=24), which is considerably lower than the proportion of vaginal deliveries of all births occurring in 2016 (52.2%).

One third of the deliveries were instrumental (33.3%, n=24 of 72), with four mothers who had a combination of a ventouse and a forceps delivery. The interval time from decision to the instrumental delivery was known in 21 of the 22 cases. The median interval time to delivery was 5 minutes and ranged from one to 12 minutes.

Caesarean section was the most common mode of delivery for all 72 of these infants (37.5%, n=27), with a slightly higher proportion of caesarean sections happening pre-labour (48.1%, n=13 of 27) rather than after the onset of labour (51.9%, n=14 of 27).

Three mothers had a caesarean section following failed instrumental deliveries. The interval time between attempting and the decision to abandon the instrumental delivery was between 5 and 16 minutes for these three mothers. The interval time from the abandonment of the instrumental delivery to caesarean section was between 15 and 26 minutes for these three mothers.

Table 20: Mode of delivery for mothers whose infants underwent therapeutic hypothermia in 2019

TH cases 2019	Total N=72	Nulliparous N=43	Parous N=29	All births*** 2016-2019[19]	
Spontaneous Vaginal Cephalic Spontaneous Vaginal Breech	22(30.6) 2(2.8)	9(20.9) 1(2.3)	13(44.8) 1(3.4)	**Vaginal birth+**	51.8%
Pre-labour Caesarean Section Caesarean Section*	13(18.1) 14(19.4)	9(20.9) 10(23.3)	4(13.8) 4(13.8)	**Caesarean section++**	33.2%
Assisted breech	0(0.0)	0(0.0)	0(0.0)	**Assisted breech**	0.1%
Ventouse**	19(26.4)**	13(30.2)	6(20.7)	**Ventouse**	11.2%
Forceps	9(12.5)	7(16.3)	2(6.9)	**Forceps**	3.7%

Note: Values are n(%) unless otherwise stated. Categories are not mutually exclusive. +Vaginal births in this category include mothers who had both a Spontaneous Vaginal Cephalic and a Spontaneous Vaginal Breech delivery. ++Caesarean section in this category include mothers who had a pre-labour caesarean section as well as mothers who had a caesarean section after the onset of labour. *Three mothers had a caesarean section following failed instrumental deliveries. **Four mothers who had a ventouse delivery, also had a forceps delivery. ***All births data are based on HIPE data and therefore relate to all mothers who gave birth in hospital rather than all births. The value for forceps includes mothers whose delivery involved both Ventouse and forceps.

The type of caesarean section was documented for all 27 mothers (Table 21). One mother whose infant underwent TH in 2019 had an elective caesarean section (3.7%; n=1 of 27). Ten mothers had an urgent caesarean section (37.0%; n=10 of 27). Emergency caesarean section delivery was the most common type of caesarean section delivery, accounting for 59.3% of cases where the infant was delivered by caesarean section (n=16 of 27). Of the mothers who had an emergency caesarean section delivery, 56.3% (n=9 of 16) were pre-labour and 43.7% (7 of 16) occurred after the onset of labour.

Table 21: Type of caesarean section delivery for mothers whose infants underwent therapeutic hypothermia in 2019

	Total N=27	Nulliparous N=19	Parous N=8
Elective – planned	1(3.7)	1(5.1)	0(0.0)
Urgent – maternal or fetal compromise which is not immediately life threatening	10(37.0)	8(42.1)	2(25.0)
Emergency – immediate threat to life of woman or fetus	16(59.3)	10(52.6)	6(75.0)

For mothers who had their labours induced, almost half had an instrumental delivery (46.2%; n=12 of 26). As outlined in Table 22, induced parous mothers were almost twice as likely to deliver vaginally compared to induced nulliparous mothers (44.4%; n=4 of 9 versus 23.5%; n=4 of 17).

Table 22: Mode of delivery for mothers who were induced whose infants underwent therapeutic hypothermia in 2019

TH cases 2019	Total N=26	Nulliparous N=17	Parous N=9
Vaginal delivery	8(30.7)	4(23.5)	4(44.4)
Caesarean Section*	7(26.9)	5(29.4)	2(22.2)
Ventouse**	7(26.9)	5(29.4)	2(22.2)
Forceps	6(23.1)	5(29.4)	1(11.1)

Note: Values are N(%) unless otherwise stated. Categories are not mutually exclusive. *One mother had a caesarean section following failed instrumental deliveries. **One mothers who had a ventouse delivery, also had a forceps delivery

Other incidents at birth and following delivery

As outlined in Table 23, 12.5% of mothers whose infants underwent TH had a shoulder dystocia (n=9). In 2019, one in ten mothers experienced maternal pyrexia during labour (n=7).

Table 23: Other incidents at the birth of infants who underwent therapeutic hypothermia in 2016-2019

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=72 2019	TH cases N=281 2016-2019
Maternal pyrexia in labour	14(22.2)	12(15.6)	3(4.3)	7(9.7)	36(12.8)
Shoulder dystocia	10(15.9)	8(10.4)	9(13.0)	9(12.5)	36(12.8)
Prolonged rupture of membranes	7(11.1)	7(9.1)	9(13.0)	3(4.2)	26(9.3)
Meconium aspiration	4(6.3)	11(14.3)	0(0.0)	4(5.6)	19(6.8)
Subgaleal haematoma	1(1.6)	2(2.6)	0(0.0)	1(1.4)	4(1.4)
Spontaneous premature labour	0(0.0)	1(1.3)	0(0.0)	0(0.0)	1(0.4)
Birth trauma	1(1.6)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Other	3(4.8)	2(2.6)	2(2.9)	(0.0)	7(2.5)

Note: Values are shown as N (%) unless otherwise stated. Categories are not mutually exclusive

Shoulder dystocia infants

Shoulder dystocia was reported as affecting the delivery of nine of the 72 infants (12.5%) who received TH in 2019, which is similar to the previous three years. In total, shoulder dystocia was associated with the delivery of 36 of the 281 infants (12.8%) who received TH in 2016-2019. In contrast, shoulder dystocia was diagnosed for 0.8% (n=1,855) of the population of 240,472 mothers who gave birth in hospital in 2016-2019 according to HIPE data. Based on these data, the risk of an infant receiving TH was 19.4 (95% CI=13.6-26.9) per 1,000 women if the delivery was affected by shoulder dystocia compared to 1.0 (95% CI=0.9-1.2) per 1,000 women if there was no reported should dystocia, a 19-fold difference (Risk ratio=18.90, 95% CI=13.32-26.82, p-value<0.001).

Table 24 details maternal, infant and delivery characteristics for the 36 cases of TH associated with shoulder dystocia compared to the other 245 cases during 2016-2019. Cases associated with shoulder dystocia were similar to other cases with respect to maternal age (p-value=0.982) and mode of delivery (p-value=0.499). The preponderance of nulliparous mothers was more evident among cases associated with shoulder dystocia but this was not statistically significant (p-value=0.175). More pronounced differences were observed related to overweight/obesity (77.8% vs. 55.2%, p-value<0.011), induction of labour (58.3% vs. 31.0%; p-value=0.001) and birthweight (55.6% ≥4kg vs. 13.9%, p-value<0.001; 30.6% ≥90th centile vs. 7.8%, p-value<0.001).

The most common manoeuvre utilised for deliveries with shoulder dystocia was a combination of McRoberts and suprapubic pressure (n=25 of 36, 69.4%). Twenty-nine of the 36 mothers had an instrumental delivery (80.6%). Time between decision to use instrumentation and delivery of the baby was recorded for the TH cases with shoulder dystocia in 2019. The median time was 5 minutes and the range was 1-12 minutes.

Table 24: Maternal, infant and delivery characteristics for deliveries with and without shoulder dystocia

Characteristic	Cases with shoulder dystocia in 2019 N=9	Cases with shoulder dystocia in 2016-2019 N=36	Cases without shoulder dystocia in 2016-2019 N=245
Age Group			
<30yrs	2(22.2)	10(27.8)	70(28.7)
30-34yrs	4(44.4)	14(38.9)	88(36.1)
35-39yrs	2(22.2)	10(27.8)	69(28.3)
>40yrs	1(11.1)	2(5.6)	17(7.0)
BMI Category (kg/m²)			
Underweight (<18.5)	0(0.0)	0(0.0)	3(1.3)
Healthy (18.5-24.9)	0(0.0)	8(22.2)	100(43.5)
Overweight (25.0-29.9)	2(22.2)	12(33.3)	66(28.7)
Obese (≥30.0)	7(77.8)	16(44.4)	61(26.5)
Parity			
Nulliparous	5(55.6)	25(69.4)	141(57.6)
Parous	4(44.4)	11(30.6)	104(42.4)
Induction of labour	6(66.7)	21(58.3)	76(31.0)
Mode of delivery			
Spontaneous Vaginal Cephalic	2(22.2)	7(19.4)	60(24.6)
Instrumental	7(77.8)	29(80.6)	184(75.4)
Manoeuvres*			
McRoberts	0(0.0)	4(11.1)	–
McRoberts and Suprapubic pressure	7(77.8)	25(69.4)	–
Other	2(22.2)	9(25.0)	–
Birthweight (grams)			
<3000	0(0)	0(0)	69(28.2)
3000-3499	0(0)	4(11.1)	73(29.8)
3500-3999	5(55.6)	12(33.3)	76(31.0)
≥4000	4(44.4)	20(55.6)	27(11.0)
Birthweight centile			
<10th	0(0)	0(0)	49(20.0)
10-49th	2(22.2)	10(27.8)	102(41.6)
50-89th	4(44.4)	15(41.7)	75(30.6)
≥90th	3(33.3)	11(30.6)	19(7.8)

Note: Values are shown as n(%) unless otherwise stated. Maternal age, body mass index (BMI) and mode of delivery were not recorded for one, 15 and one case, respectively. *Categories are not mutually exclusive

Infant characteristics

Two-thirds of the infants who received TH in 2019 were female (65.3%; n=47 of 72). In the overall population of births in 2016, 51.3% were male and 48.7% female (Table 25). There were two infants who underwent TH from multiple births (2.8%). This is slightly lower than the proportion of multiples among all births in 2016 (3.8%).[10]

Table 25: Sex of infants who underwent therapeutic hypothermia in 2016-2019

	TH cases N=63 2016	TH cases N=77 2017	TH cases N=69 2018	TH cases N=72 2019	TH cases N=281 2016-2019	All births[19] 2016-2019
Male	32(50.8)	48(62.3)	53(76.8)	25(34.7)	158(56.2)	51.3%
Female	31(49.2)	29(37.7)	16(23.2)	47(65.3)	123(43.8)	48.7%

Note: Values are shown as N(%) unless otherwise stated

Gestation at delivery

Figure 3 outlines the gestational age at delivery for infants who underwent TH in 2019 versus all infants born in 2016[17]. Almost two thirds of infants were born between 40 and 42 completed weeks gestation (61.1%; n=44 of 72).

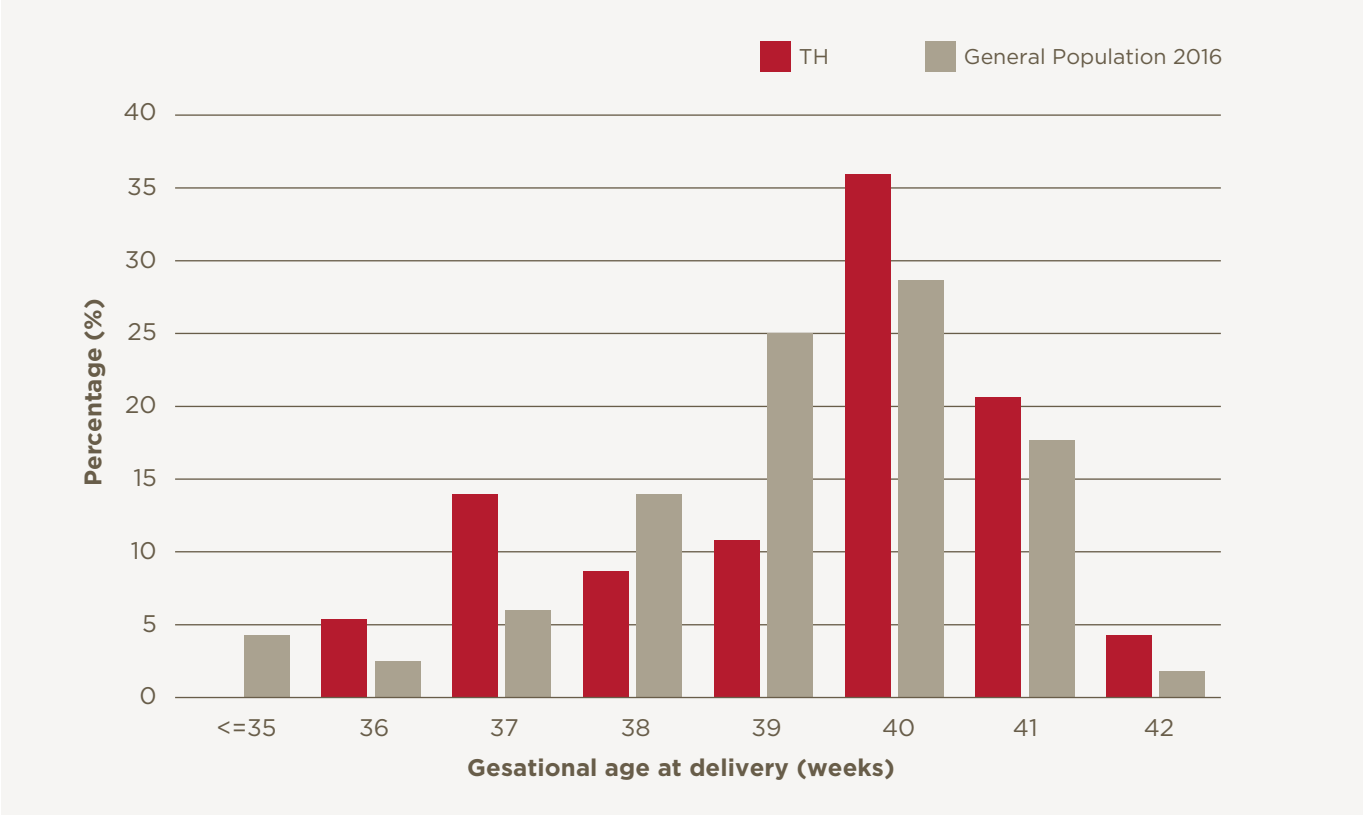


Figure 3: Gestational age at delivery (weeks) for infants who underwent therapeutic hypothermia in 2019 versus all infants born in 2016

Birthweight at delivery

The mean birthweight for infants who underwent neonatal TH in 2019 was 3,431 grams (Standard Deviation: 629 grams). The birth weight ranged from 1,680 grams to 5,380 grams. As outlined in Figure 4, almost a third of infants weighed 3,000-3,499 grams (29.2%, n=21). Almost half of infants weighed 3,500 grams or more (47.2%, n=34). A small proportion of infants weighed between 1,680 and 2,499 grams (5.6%, n=4) and of these four infants, two had an antenatal diagnosis of fetal growth restriction (50.0%; n= 2 of 4).

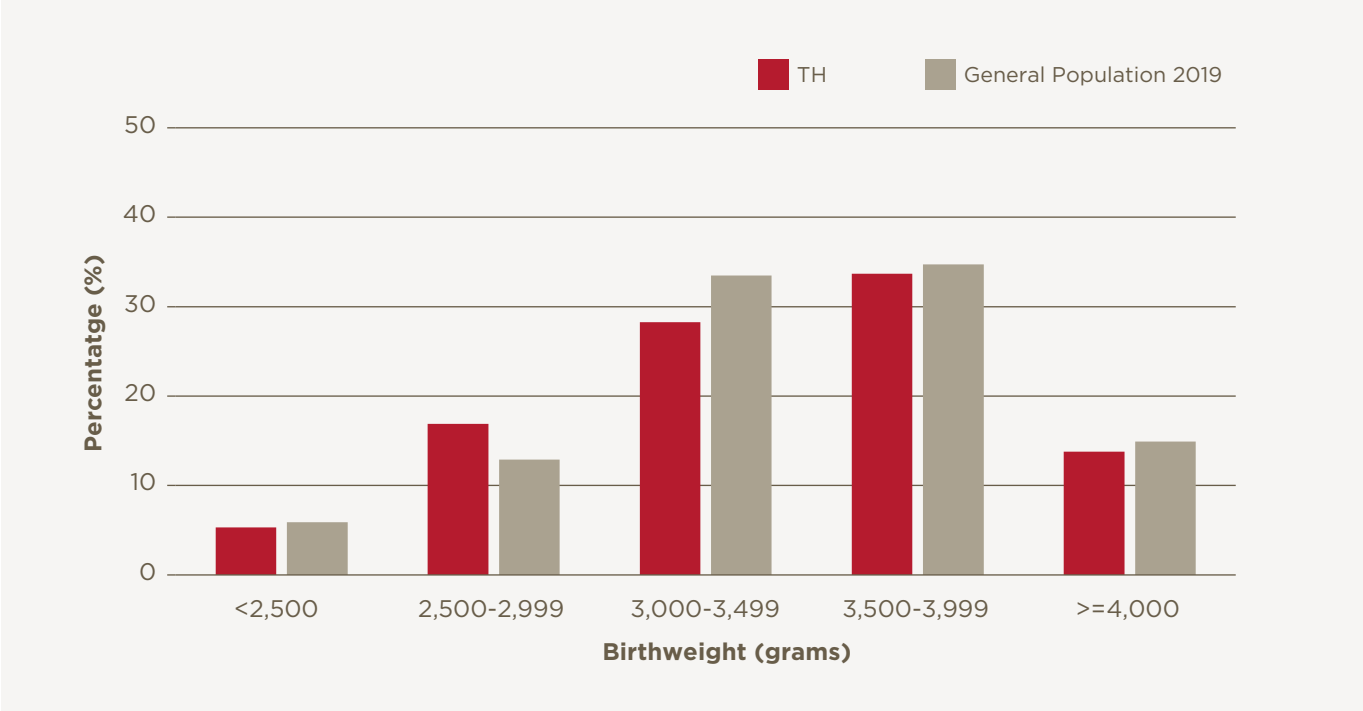


Figure 4: Distribution of birthweight for infants who underwent therapeutic hypothermia in 2019 versus all infants born in 2019

Birthweight Centiles

Gestation Related Optimal Weight (GROW) software and coefficients derived from the multiple regression analysis of data on 11,072 births in six maternity units in Dublin, Galway, Limerick and Belfast in 2008-2009, was used to produce Figure 5[20] which illustrates the optimal birthweight and normal range compared to the recorded birthweights of infants who underwent neonatal TH in 2019.

The optimal weight and normal range for all gestations are plotted with the actual birthweights of the infants in Figure 6. As can also be seen in Table 21, one in six of these infants were below the lower limit of the normal range (10th centile).

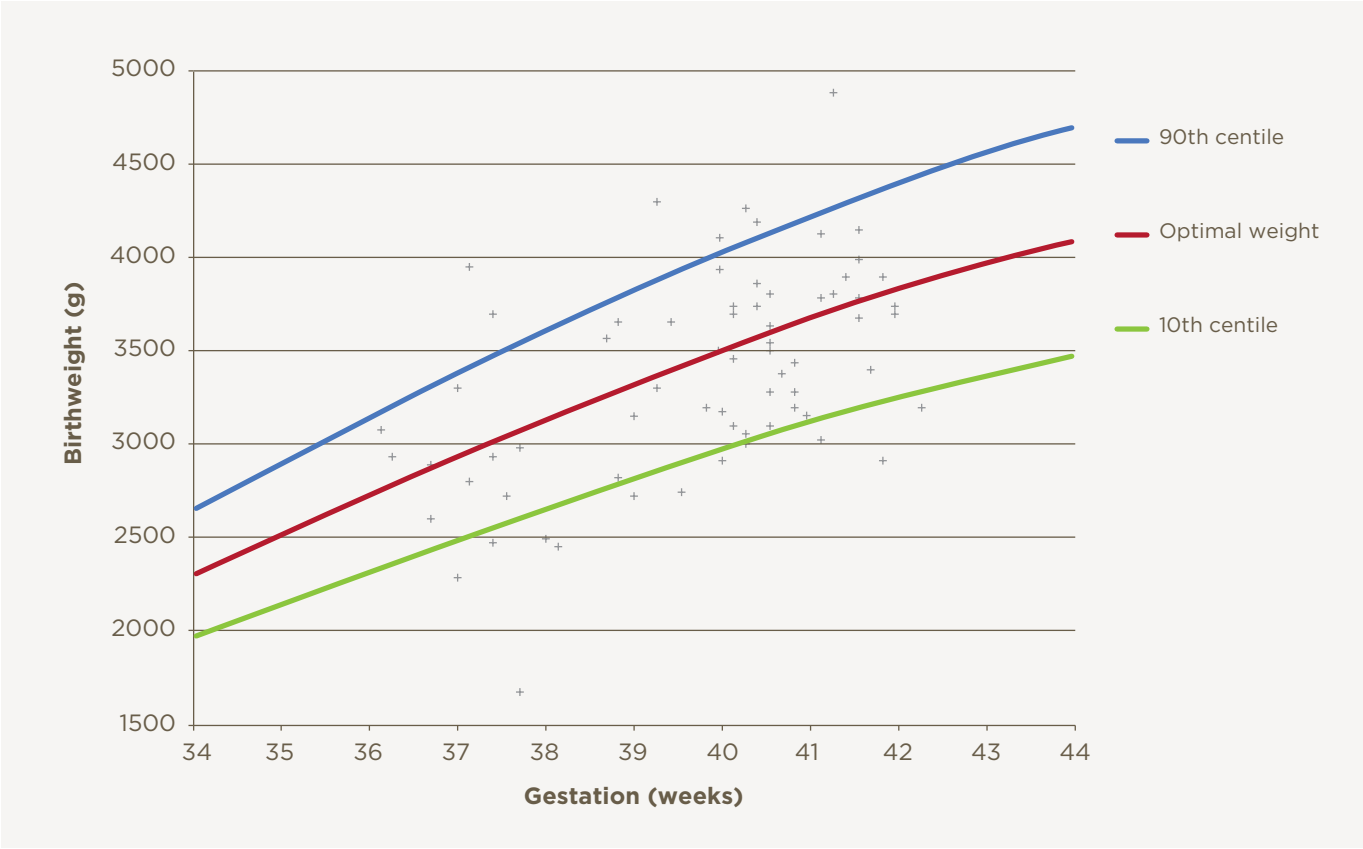


Figure 5: Optimal birthweight and normal range compared to actual birthweights for infants who underwent therapeutic hypothermia in 2019

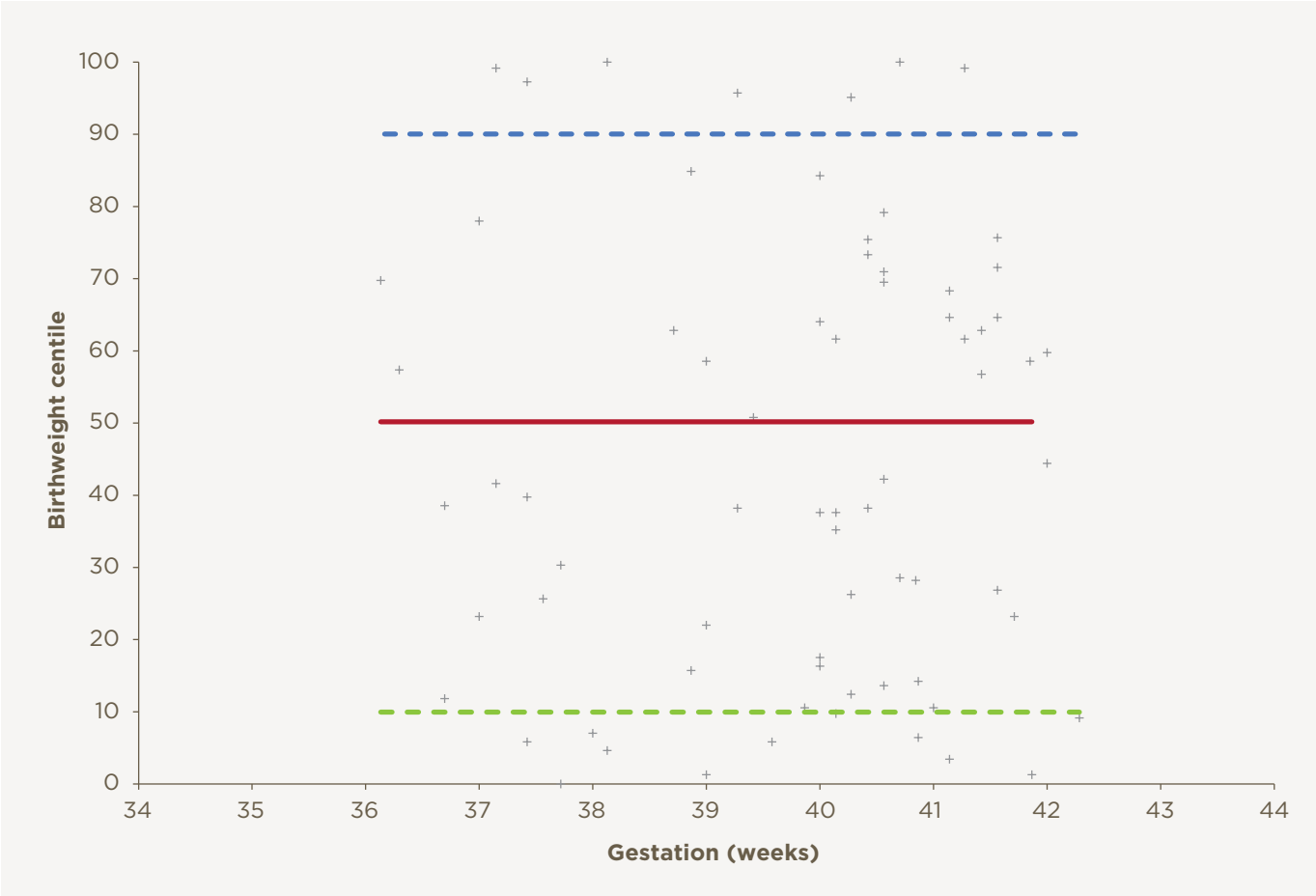


Figure 6: Distribution of customised birthweight centiles for infants who underwent therapeutic hypothermia in 2019

When examined by birth weight centile category, the distribution of the TH cohort was broadly similar to that expected but there was some evidence of poor fetal growth. Almost 20% of the infants (n=49, 17.4%) in 2016-2019 were below the 10th centile.

Table 26: Birth weight centiles for infants who underwent therapeutic hypothermia in 2016-2019

Centiles	TH cases 2016 N=63	TH cases 2017 N=77	TH cases 2018 N=69	TH cases 2019 N=72	TH cases 2016-2019 N=281
<3rd	2(3.2)	6(7.8)	4(5.8)	3(4.2)	15(5.3)
3rd to 9th	7(11.1)	11(14.3)	8(11.6)	8(11.1)	34(12.1)
10-49th	27(42.9)	28(36.4)	28(40.6)	29(40.3)	112(39.9)
50-89th	17(27.0)	24(31.2)	24(34.8)	25(34.7)	90(32.0)
≥90th	10(15.9)	8(10.4)	5(7.2)	7(9.7)	30(10.7)

Note: Values are shown as N(%) unless otherwise stated

Table 27: Birth weight centiles for infants who underwent therapeutic hypothermia in 2016-2019

Centiles	TH cases 2019 N=72	TH cases 2016-2019 N=281	Rate (95% CI)	Rate ratio (95% CI)	P-value
<3rd	3(4.2)	15(5.3)	1.99(1.47-2.63)	2.18(1.54-3.08)	<0.001
3rd to 9th	8(11.1)	34(12.1)			
10-49th	29(40.3)	112(39.9)	1.14(0.94-1.37)	1.24(0.94-1.64)	0.122
50-89th	25(34.7)	90(32.0)	0.91(0.73-1.12)	1.00(ref.)	
≥90th	7(9.7)	30(10.7)	1.22(0.82-1.74)	1.33(0.88-2.02)	0.172

Note: Values are shown as N(%) unless otherwise stated

Based on the four years of data from 2016-2019, there was significant variation in risk of TH associated with birthweight centile (Table 27). Infants with a birthweight in the 50-89th centile range had the lowest risk of TH, at 0.91 per 1,000 births. The risk was 24% and 33% higher among infants in the 10-49th and >90th birthweight centile ranges, respectively, but the risk was doubled for infants with a birthweight under the 10th centile.

Diagnosis of fetal growth restriction (FGR)

Data on diagnosis of FGR were recorded for all 72 infants who underwent TH in 2019 (100%). Five (6.9%) of the 72 infants in 2019 had a diagnosis of FGR in their medical records (Table 28) and for all five the diagnosis was made in the antenatal period (as opposed to diagnosis based on observation at delivery or post-mortem). Of those with an antenatal diagnosis of FGR, two had a birthweight below the 10th centile and the remaining three had birthweights between the 10th and 49th birthweight centiles.

As previously illustrated in Table 26, there were 11 infants who underwent therapeutic hypothermia in 2019 born with a birth weight below the 10th centile. Only two of these 11 infants had a diagnosis of FGR during the antenatal period, at delivery or post-mortem (18.1%; n=2 of 11).

Table 28: Diagnosis of fetal growth restriction for infants who underwent therapeutic hypothermia in 2016 -2019

	TH cases 2016 N=63	TH cases 2017 N=74*	TH cases 2018 N=69	TH cases 2019 N=72	TH cases 2016-2019 N=278*
No diagnosis documented	60(95.2)	66(89.2)	64(92.8)	67(93.1)	258(92.8)
Diagnosis of fetal growth restriction	3(4.8)	8(10.8)	5(7.2)	5(6.9)	20(7.2)
Fetal growth restriction suspected antenatally	1 of 3(33.3)	5 of 8(62.5)	3 of 5 (60.0)	5 of 5 (100)	13 of 20(65.0)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for three infants

Resuscitation

Neonatal or paediatric support was called prior to the delivery of three quarters of cases (76.1%; n=54 of 71; missing data for one infant born before arrival). As outlined in Table 29, a registrar was present at the vast majority of births for resuscitation (90.1%; n=64 of 71; data missing for one infant). A Senior House Officer (SHO) was also present at the majority of births for resuscitation (78.9%; n=56 of 71). A neonatal nurse was present at 40% of births (n=28 of 71). A consultant was present for 41% of births for resuscitation (40.8%; n=29 of 71).

Table 29: Medical staff present at the time of birth for the resuscitation of infants who underwent therapeutic hypothermia in 2016-2019

	TH cases 2016 N=61*	TH cases 2017 N=77	TH cases 2018 N=68**	TH cases 2019 N=71**	TH cases 2016-2019 N=277
Consultant(Neonatology/Paediatrics)	21(34.4)	27(35.1)	28(41.2)	29(40.8)	105(37.9)
Registrar	56(91.8)	73(94.8)	60(88.2)	64(90.1)	253(91.3)
Senior House Officer	48(78.7)	68(88.3)	63(92.6)	56(78.9)	230(83.0)
Neonatal Nurse	22(36.1)	37(48.1)	36(52.9)	28(39.4)	123(44.4)
Midwife	16(26.2)	17(22.1)	11(16.1)	16(22.5)	60(21.7)

Note: Values are shown as N(%) unless otherwise stated. *Data missing for two infants. **Data missing for one infant. Categories are not mutually exclusive. These data should be interpreted with caution as documentation related to grade of those in attendance was poorly recorded in maternity notes

As indicated in Table 30, at one minute after birth over three quarters of infants (82.6%; n= 57 of 69) had an Apgar score of between zero and three. At ten minutes, infants with an Apgar score of between zero and three had reduced to 31.3% (n=20 of 64). At twenty minutes, only three infants had an Apgar score recorded; all of whom had a score of two or lower.

Table 30: Apgar Scores at 1, 5, 10, 15 and 20 minutes for infants who underwent therapeutic hypothermia in 2019

	1 minute N=69	5 minutes N=70	10 minutes N=64	15 minutes N=16	20 minutes N=3
0	13(18.8)	10(14.3)	4(6.3)	2(12.5)	2(66.7)
1	23(33.3)	7(10.0)	8(12.5)	1(6.3)	0(0)
2	14(20.3)	5(7.1)	4(6.3)	1(6.3)	1(33.3)
3	7(10.1)	10(14.3)	4(6.3)	1(6.3)	0(0)
4	6(8.7)	14(20.0)	8(12.5)	3(18.8)	0(0)
5	1(1.4)	7(10.0)	11(17.2)	1(6.3)	0(0)
6	2(2.9)	6(8.6)	8(12.5)	1(6.3)	0(0)
7	2(2.9)	3(4.3)	9(14.1)	3(18.8)	0(0)
8	0(0)	6(8.6)	5(7.8)	2(12.5)	0(0)
9	1(1.4)	1(1.4)	3(4.7)	1(6.3)	0(0)
10	0(0)	1(1.4)	0(0)	0(0)	0(0)

Note: Values are shown as N(%) unless otherwise stated

An Apgar chart was completed for 55.6% (n=40) of infants at one minute of life; 55.6% (n=40) of infants at five minutes of life; 50.0% (n=36) infants at 10 minutes of life and 18.1% (n=13) infants at 15 minutes of life (Table 31).

Table 31: Apgar Charts at 1, 5, 10 and 15 minutes for infants who underwent therapeutic hypothermia in 2019

	1 minute N=40	5 minutes N=40	10 minutes N=36	15 minutes N=13
Heart rate				
Absent	7(17.5)	6(15.0)	2(5.6)	1(7.7)
<100	17(42.5)	5(12.5)	7(19.4)	1(7.7)
>100	16(40.0)	29(72.5)	27(75.0)	11(84.6)
Respiration effort				
Absent	31(77.5)	21(52.5)	13(36.1)	6(46.2)
Slow irregular	7(17.5)	14(35.0)	14(38.9)	3(23.1)
Regular crying	2(5.0)	5(12.5)	9(25.0)	4(30.8)
Muscle tone				
Limp	34(85.0)	28(38.9)	22(61.1)	6(46.2)
Some flexion	4(10.0)	9(22.5)	13(36.1)	5(38.5)
Active Movement	2(5.0)	3(7.5)	1(2.8)	2(15.4)
Stimulus catheter				
Nil	32(80.0)	26(65.0)	18(50.0)	6(46.2)
Grimace	6(15.0)	8(20.0)	15(41.7)	3(23.1)
Cough/sneeze	2(5.0)	6(15.0)	3(8.3)	4(30.8)
Colour				
Nil	29(72.5)	13(32.5)	10(27.8)	2(15.4)
Pink body, blue extremities	9(22.5)	22(55.0)	15(41.7)	8(61.5)
Pink	2(5.0)	5(12.5)	11(30.6)	3(23.1)

Note: Values are shown as N(%) unless otherwise stated

In 2019, the majority of infants had positive pressure ventilation (PPV) during resuscitation (91.7%; n=66 of 72) which began between zero and nine minutes and was sustained between one and 20 minutes. Spontaneous breathing was established by almost half of infants (45.8%; n=33 of 72). Of these infants, the age at which spontaneous breathing was sustained was recorded for 21 of the 33 infants (66.3%) and began between 2 and 10 minutes (median 4 minutes).

As illustrated in Table 32, two thirds of the 72 infants were intubated (63.9%; n=46) which occurred between 1 and 19 minutes. One third of infants had chest compressions (38.9%, n=28), which began between 0 and 14 minutes (data missing for four infants). FiO_2 was administered to the majority of infants (88.9%, n=64)

Table 32: Resuscitation for infants who underwent therapeutic hypothermia in the years 2016-2019

	TH cases 2016 N=63	TH cases 2017 N=77	TH cases 2018 N=69	TH cases 2019 N=72	TH cases 2016-2019 N=280
Positive pressure ventilation	-	-	-	66(91.7)	-
Spontaneous breathing established	37(58.7)	37(48.1)	36(52.2)	33(45.8)	143(51.1)
Intubation	32(50.8)	50(64.9)	41(59.4)	46(63.9)	170(60.7)
Chest compressions	19(30.2)	28(36.4)	23(33.3)	28(38.9)	98(35.0)
FiO_2	57(90.5)	72(93.5)	61(89.7)	61(89.7)	254(90.7)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

Table 33: Drugs or fluid treatment administered at birth for infants who underwent therapeutic hypothermia in 2016-2019

	TH cases 2016 N=63	TH cases 2017 N=77	TH cases 2018 N=69	TH cases 2019 N=72	TH cases 2016-2019 N=281
Adrenaline	9(14.3)	9(11.7)	11(15.9)	13(18.1)	42(14.9)
Saline	21(33.3)	21(27.3)	12(17.4)	17(23.6)	81(28.8)
O negative blood	5(7.9)	8(10.4)	2(2.9)	4(5.6)	19(6.8)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

One of the key indicators for intrapartum asphyxia is severe metabolic acidosis evident in umbilical cord blood at delivery[21]. A cord blood gas measurement was available for 84.7% of infants (n=61). As outlined in Table 34, two thirds of infants had a pH of <7.0 from their arterial blood gas (65.4%, n=34 of 52). The median base excess was -11.8 (Range: -4.6 to-24.0) from cord blood gases and was -15.9 (Range: -1.5 to -34.8) from initial infant blood gases. Lactate was recorded for 31.9% of infants (n=23) from cord blood gases and for 91.7% of infants (n=66) from the initial infant blood gas.

Table 34: pH level from cord and initial infant blood gases for infants who underwent therapeutic hypothermia in 2019

	Cord Blood Gas			Initial Infant Blood Gas		
	Venous N=58	Capillary N=52	Unknown N=3	Venous N=38	Capillary N=12	Arterial N=20
pH level						
6.4-6.5	0(0.0)	1(1.9)	0(0.0)	0(0.0)	(0.0)	0(0.0)
6.51-6.6	1(1.7)	0(0.0)	0(0.0)	2(5.3)	1(8.3)	6(30.0)
6.61-6.7	1(1.7)	0(0.0)	0(0.0)	2(5.3)	2(16.7)	0(0.0)
6.71-6.8	6(10.3)	8(15.4)	0(0.0)	3(7.9)	3(25.0)	3(15.0)
6.81-6.9	5(8.6)	13(25.0)	1(33.3)	5(13.2)	3(25.0)	2(10.0)
6.91-7.0	4(6.9)	12(23.1)	0(0.0)	12(31.6)	1(8.3)	2(10.0)
7.01-7.1	9(15.5)	8(15.4)	0(0.0)	6(15.8)	1(8.3)	0(0.0)
7.11-7.2	15(25.9)	10(19.2)	0(0.0)	6(15.8)	1(8.3)	3(15.0)
7.21-7.3	15(25.9)	0(0.0)	1(33.3)	2(5.3)	0(0.0)	3(15.0)
7.31-7.4	2(3.4)	0(0.0)	1(33.3)	0(0.0)	0(0.0)	1(5.0)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

Assessment for Therapeutic Hypothermia

In two-thirds of cases the NNTP Cooling Candidacy Checklist was used when making an assessment for TH (66.7%; n=48 of 72). Three quarters of the mothers (68.1%), whose infants underwent TH in 2019, experienced an acute perinatal event (Table 35). Almost half of infants experienced variable and/or late fetal heart rate decelerations during labour (48.6%; n=35).

Table 35: Assessment for therapeutic hypothermia in 2019

	TH cases 2019 N=72
>36 completed weeks gestational age	**72(100)**
Apgar score ≤5 at 10 minutes	43(59.7)
Weight ≥1800 grams	71(98.6)
Continued need for PPV or Intubation at 10 mins	49(68.1)
Did an acute perinatal event occur?	**49(68.1)**
Variable / late fetal heart rate decelerations	35(48.6)
Prolapsed / ruptured / tight nuchal cord	6(8.3)
Uterine Rupture	1(1.4)
Maternal haemorrhage / placental abruption	8(11.1)
Maternal trauma	0(0)
Other	2(2.8)
Acidosis present in umbilical cord, or any blood sample within 60 minutes of birth	**45(62.5)**
Base Deficit >16.0 mmol/L in umbilical cord, or any blood sample, within 60 minutes of birth	**35(48.6)**

Note: Values are shown as N(%) unless otherwise stated

The majority of the infants (88.9%, n=64 of 72) had a diagnosis of encephalopathy based on having an altered state of consciousness, (lethargy, stupor or coma). Although not a requirement for assessment, a grade of encephalopathy was assigned to 32.8% of infants (n=21 of 64). Table 36 illustrates that almost three quarters of infants were graded as moderately encephalopathic during assessment for TH (76.2%; n=16).

Table 36: Grade of encephalopathy during assessment for therapeutic hypothermia in 2016-2019

	TH cases 2016 N=29	TH cases 2017 N=40	TH cases 2018 N=28	TH cases 2019 N=21
Mild	3(10.3)	8(20.0)	2(7.1)	0(0.0)
Moderate	17(58.6)	22(55.0)	17(60.7)	16(76.2)
Severe	9(31.0)	10(25.0)	9(32.1)	5(23.8)

Note: Values are shown as N(%) unless otherwise stated

Transfer to Tertiary Unit

For reasons of safety and expertise, the provision of Neonatal TH by means of active servo-controlled cooling, is limited in Ireland to the four tertiary neonatal intensive centres. In order that infants born outside these centres are not delayed in accessing TH within the 6 hour window, TH in Ireland is delivered by way of a continuum of care between the referring hospital, transport team and tertiary TH centre.

Utilising national guidelines and documentation,[22] TH by means of passive (or active) cooling is commenced at the referring hospital as soon as the criteria for cooling[22] have been met. The time the target temperature is reached is recorded. TH via passive cooling can then be continued during transport by own hospital teams or in those cases transported by the NNTP, utilising active servo-controlled cooling. On arrival at the tertiary centre TH via active cooling is either continued from an NNTP transfer or initiated after an own hospital transfer.

Almost two-thirds of the 72 infants who underwent neonatal TH in 2019 were born in a tertiary hospital (n=46, 63.9%; Table 37). The other 26 infants required transfer to a tertiary unit for TH treatment (36.1%). Of the 281 infants who received TH during the four-year period 2016-2019, 60% of the infants were born in a tertiary hospital (n=171 of 281, 59.8%). During the same period, according to HIPE data, 53% of all the mothers who gave birth in hospital did so in a tertiary hospital (n=126,720 of 240,472, 52.7%). Thus, TH was provided to 1.35 infants per 1,000 mothers who gave birth in a tertiary hospital (95% CI=1.15-1.57) and 0.97 infants per 1,000 mothers who gave birth in a non-tertiary hospital (95% CI=0.79-1.17), a 40% difference (Risk ratio=1.40, 95% CI=1.10-1.77, p-value=0.006).

Of the 26 infants who required transfer to a tertiary unit for TH treatment in 2019, a decision to redirect care for one infant was taken by the team before transport. The majority of 25 infants were transported by the NNTP (84.0%; n=21 of 25) with the remaining four (16.0%) infants being transported by the referring hospital's team.

Table 37: Transfer of infants to a tertiary unit for therapeutic hypothermia treatment in 2019

	TH cases 2019 N=72
Inborn at tertiary unit	46(63.9)
Out-born requiring transfer*	26(36.1)
Transferred by the NNTP	21 of 25(84.0)
Transferred by referring hospital's team	4 of 25(16.0)

Note: Values are shown as N(%) unless otherwise stated. *For one of the 26 infants requiring transfer a decision to redirect care was taken by the team before transport

For the majority of infants who required transfer, a referral call was made to the tertiary cooling centre within two hours of birth (80.0%, n=20 of 25; missing data for one infants). A call was made between two and three hours for 20.0% of infants requiring transport (n=5 of 25; missing data for one infant).

A decision to redirect care for one infant was taken by the team before transport. All 25 infants who were transferred to a tertiary centre were initially passively cooled. Passive cooling was initiated within the first hour of birth for over half of infants (54.1%; n=13 of 24; missing data for one infant). All 25 infants who were transferred to a tertiary centre, were commenced on TH at the referring hospital within six hours of birth, by means of passive cooling (16.0% ;4 of 25) and/or active cooling (84.0%; 21 of 25). TH was continued during transport in all cases where infants were transferred to a tertiary centre (100%; n= 25). All infants transferred by the NNTP were changed from passive to active cooling for transport either before or on departure from the referral hospital (100%; n=21 of 21).

As illustrated in Figure 7, three-quarters of the infants transferred had a core temperature within the target range of 33°C to 34°C on departure from the referring hospital (76.0%, n=19 of 25). One-quarter of infants (20.0%; n=5 of 25) had a core temperature ranging from 34.1°C to 37.7°C. One infant had a core temperature below 33°C.

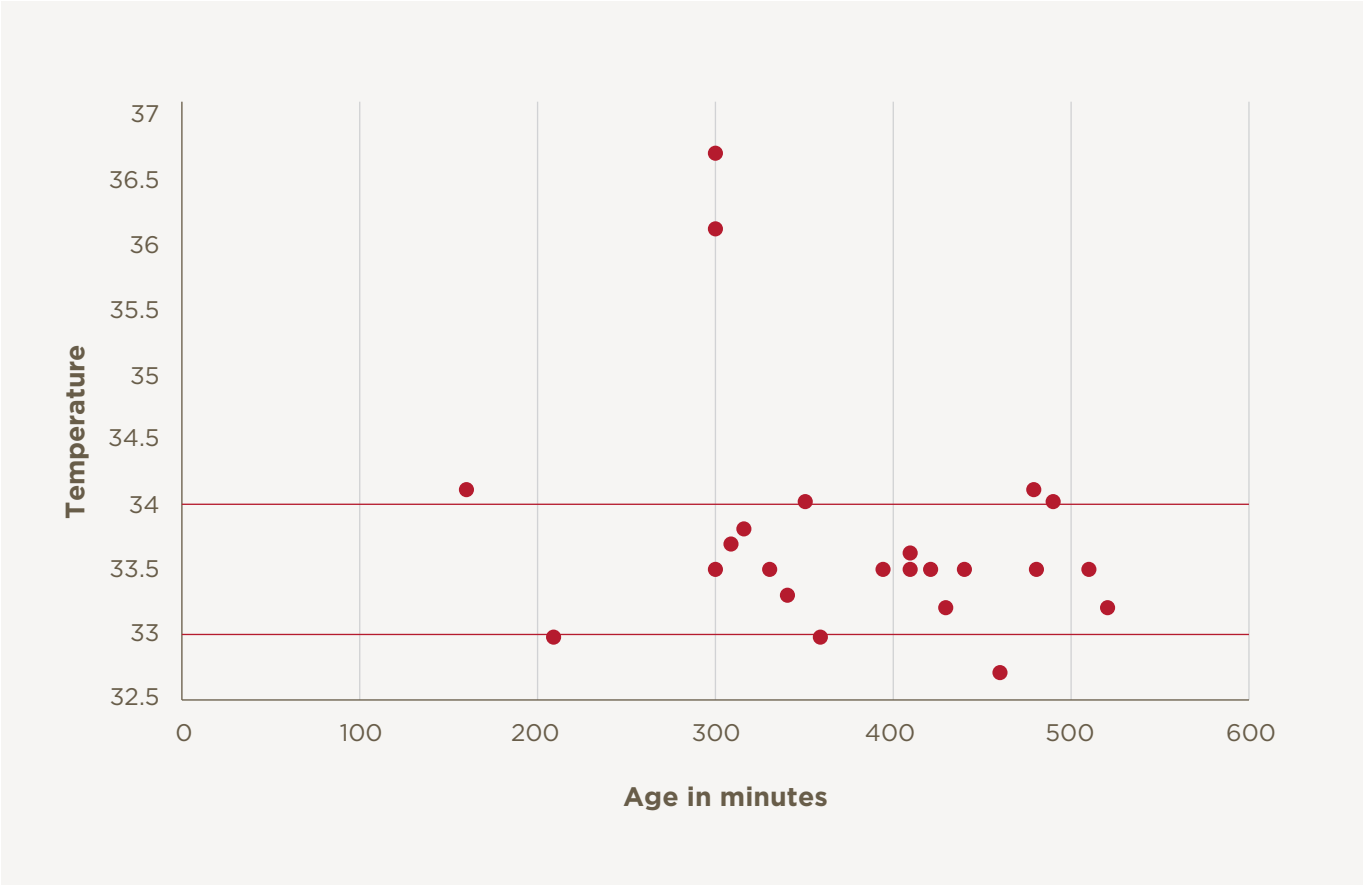


Figure 7: Temperature (°C) of infant by age (mins) on departure from referring hospital

Over three-quarters of the 25 infants transferred for neonatal TH treatment required respiratory support (80.0%; n=20) and two-thirds required sedation (64.0%; n=16) en-route to a tertiary unit (Table 38).

Table 38: Management during transfer of infants for therapeutic hypothermia in 2019

	NNTP N=21	Own Hospital Team N=4
Respiratory support	**18(85.7)**	**2(50.0)**
Ventilation	15 of 18(83.3)	1 of 2 (50.0)
CPAP	3 of 18(16.7)	1 of 2 (50.0)
Nasal prong O_2	0(0.0)	0(0)
Sedation	**16(76.2)**	**0(0)**
IV access	**21(100)**	**4(100)**
Peripheral	21 of 21(100)	4 of 4(100)
Umbilical	17 of 21(81.0)	1 of 4(25.0)
Other	1 of 21(4.8)	0(0)

Note: Values are shown as N(%) unless otherwise stated. For one of the 26 infants requiring transfer a decision to redirect care was taken by the team before transport

Eighty eight percent of the infants requiring transfer to a tertiary unit for TH treatment were admitted more than six hours after birth (88.0%; n=22 of 25). One third (32.0%; n=8 of 25) of the infants requiring transfer to a tertiary unit for neonatal TH treatment were admitted nine or more hours after birth.

As illustrated in Figure 8, the majority of infants had a core temperature within the target range of 33°C to 34°C (88.0%, n=22 of 25) on admission to a tertiary unit. The remaining 12.0% (n=3) had a core temperature ranging from 34.2°C to 34.9°C when they were admitted to the tertiary unit after six hours of birth.

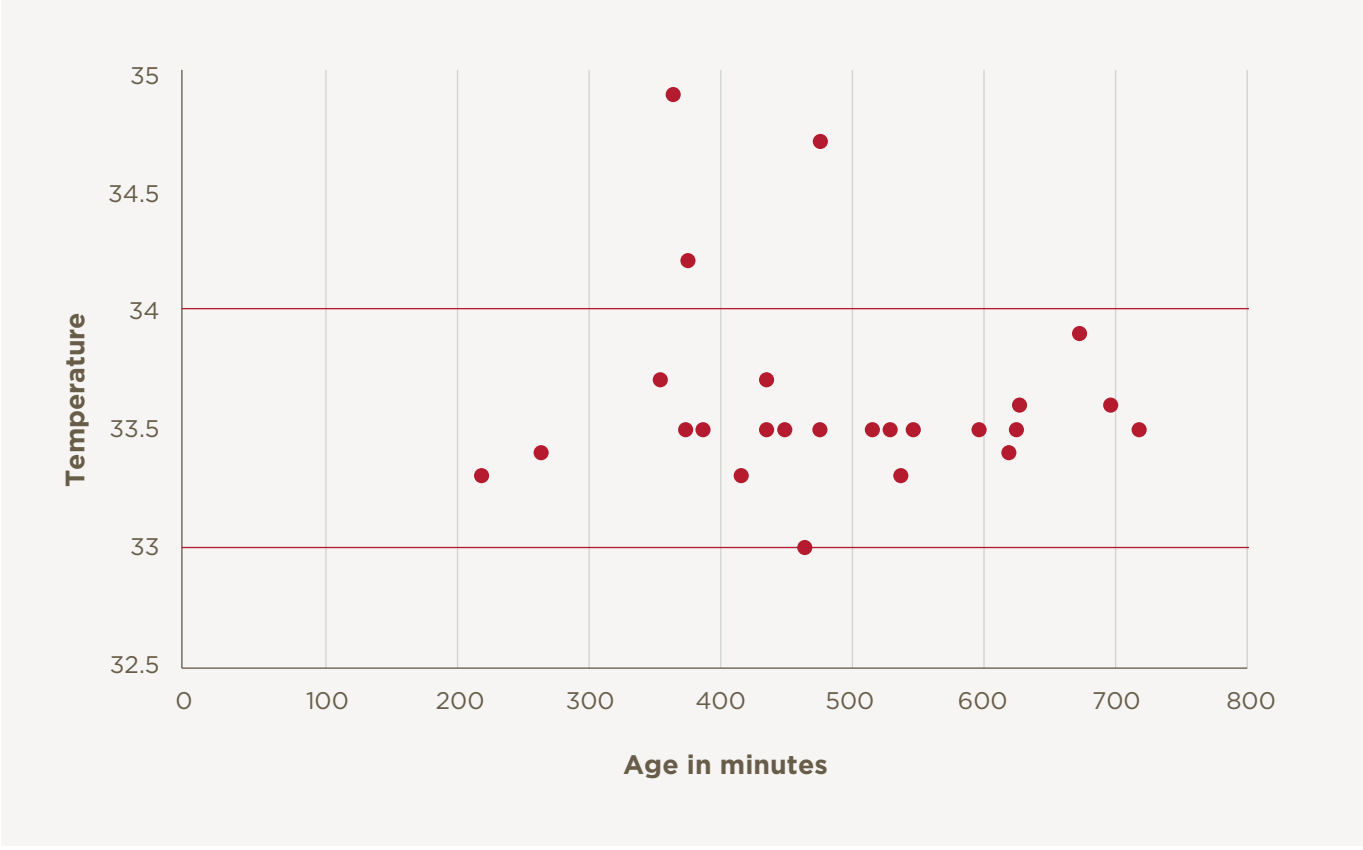


Figure 8: Temperature (°C) of infant by age (mins) on admission to a tertiary unit from a referring hospital

Initiating Treatment

In line with practice guidelines, TH should be initiated within six hours of birth and should be continued for 72 hours. The optimum core temperature of 33°C to 34°C is targeted over this 72-hour period. Core temperature was recorded for the first twelve hours of birth, or until the initiation of the 72-hour treatment clock. Of the 72 infants, half of infants (54.2%; n=39 of 72) were reported to have achieved optimum core temperature within three hours of birth. As illustrated in Figure 9 and 10, infants born in a tertiary hospital reached optimum core temperature sooner than infants that were outborn requiring transfer. These figures further illustrate that the vast majority of all infants, both inborn and outborn, achieved optimum core temperature within six hours of birth (90.3%; n=65 of 72). Optimum core temperature was achieved for the remaining 7 infants (9.7%) between 7 and 9 hours of birth.

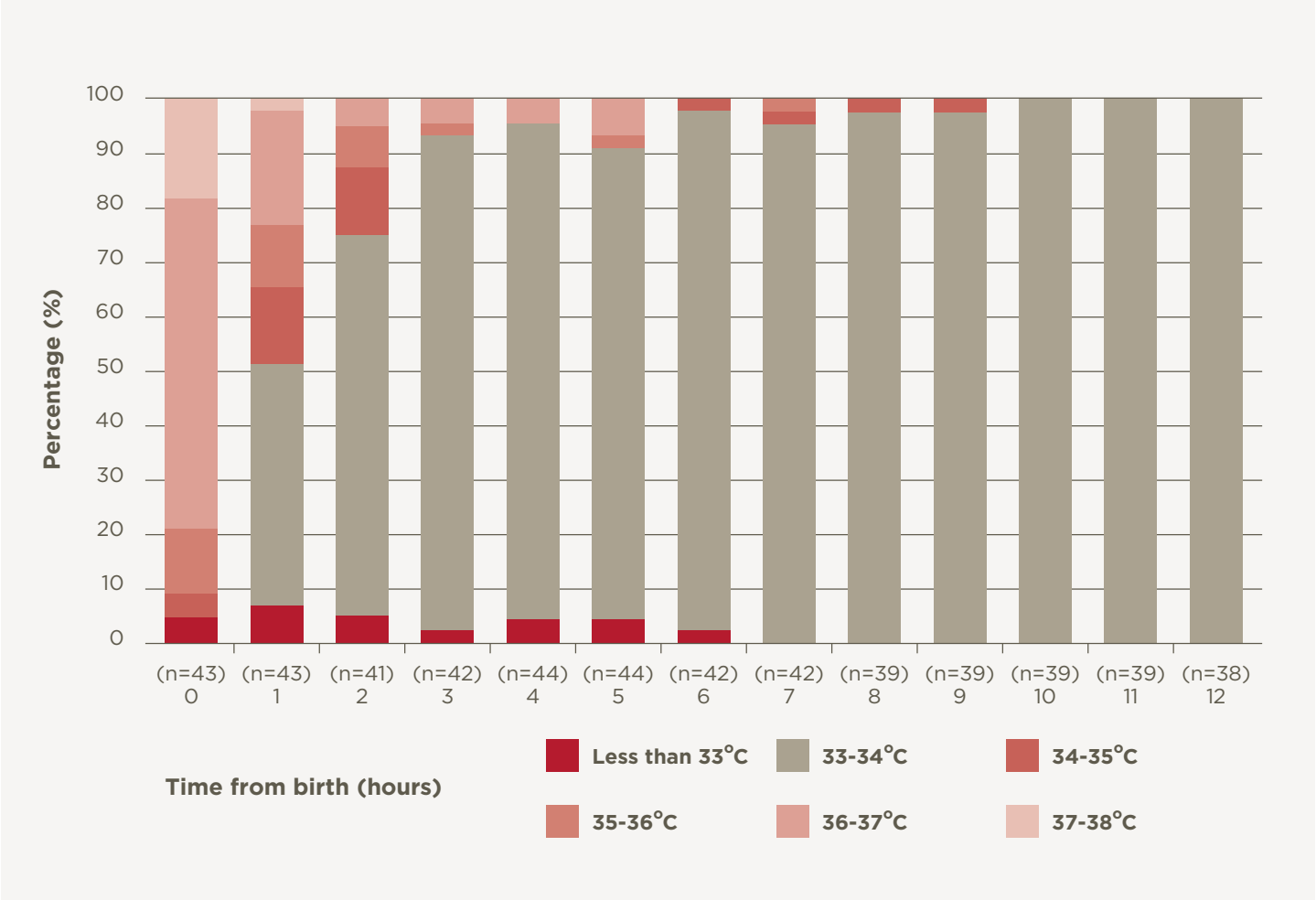


Figure 9: Infant core temperature for the first twelve hours of life for infants born in a tertiary hospital

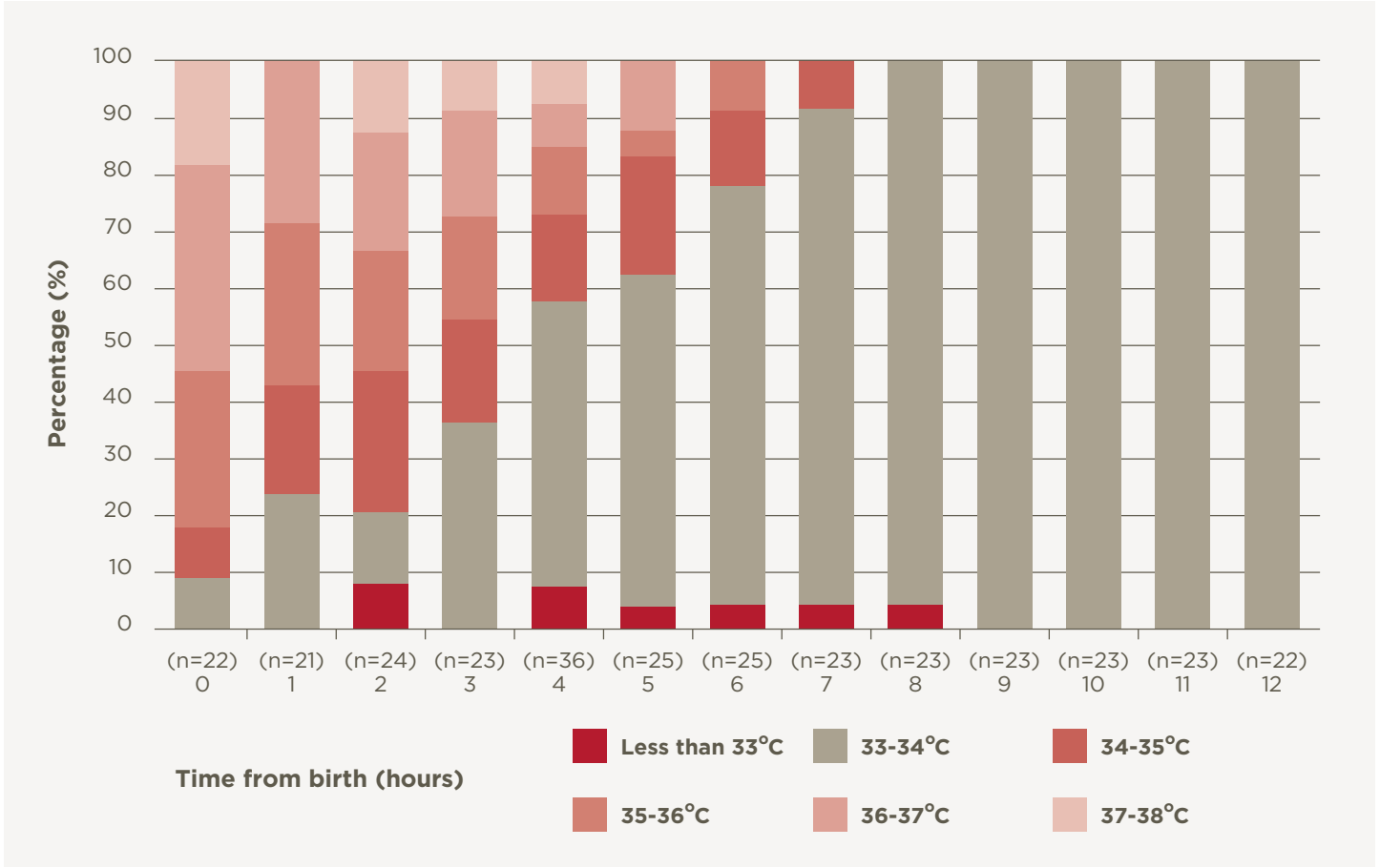


Figure 10: Infant core temperature for the first twelve hours of life for infants born in a regional hospital

The 72-hour treatment clock should begin when the infant reaches the targeted 33-34°C rectal temperature. As illustrated in Figure 11, almost two thirds of infants (60.3%; n=41 of 68: data missing for 4 infants) began TH at the optimum core temperature of 33°C to 34°C.

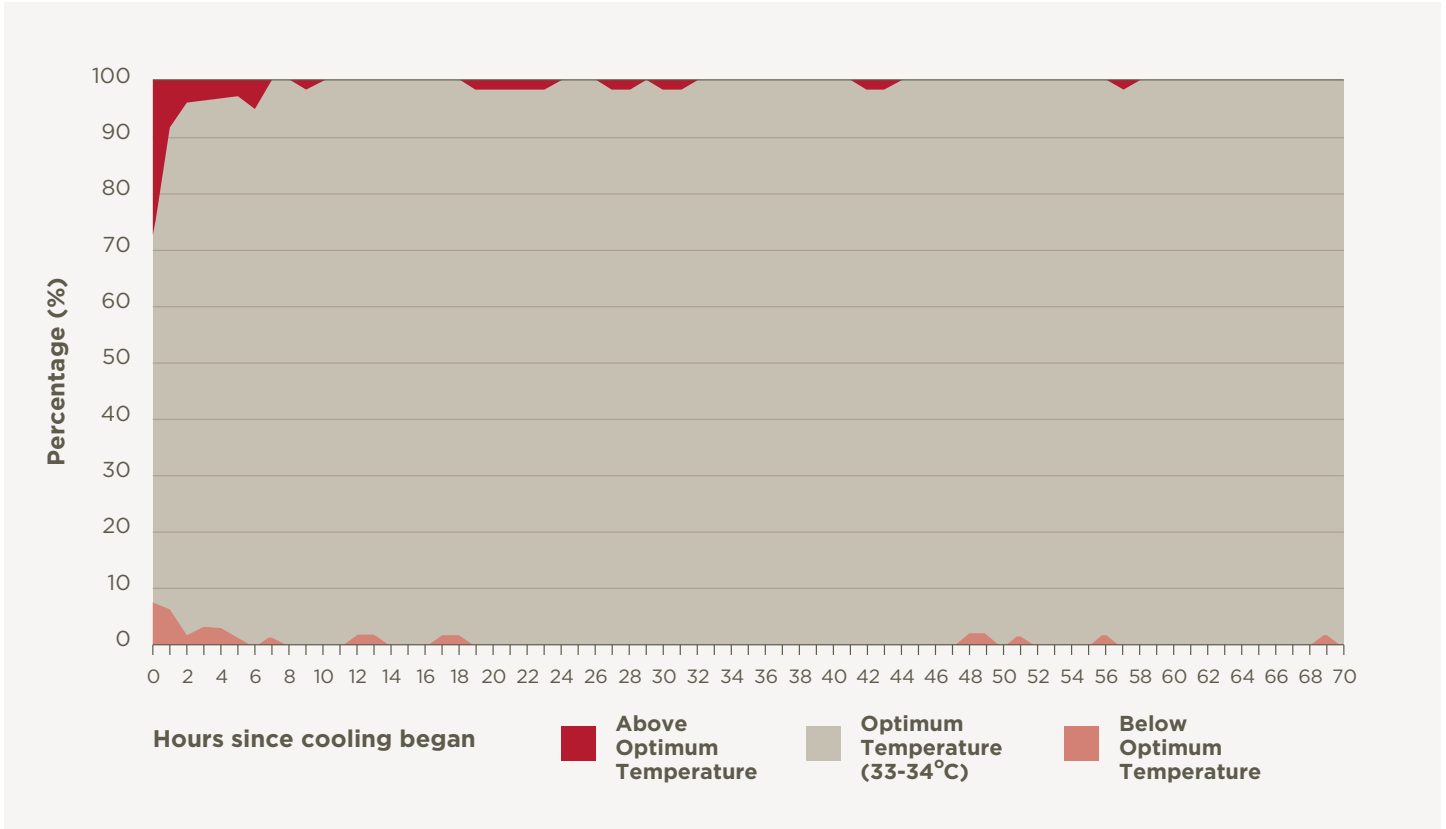


Figure 11: Percentage of infants at optimum temperature (33-34°C) over 72 hours of therapeutic hypothermia

Treatment Days 1-3

As outlined in Table 39, almost all infants admitted for neonatal therapeutic hypothermia received sedation on Day 1 (95.8%; n=69 of 72), Day 2 (88.9%; n=64 of 72) and Day 3 (80.6%; n=58 of 72) of treatment. All infants were administered antibiotics on Day 1 (100%; n=72). The vast majority of infants were administered antibiotics on Day 2 of treatment (80.6%; n=58 of 72), with almost half receiving antibiotics on Day 3 (45.8%; n=33 of 72). Twelve infants required blood products on Day 1 of treatment (16.7%) of which the majority had fresh frozen plasma administered (91.7%; n= 11 of 12) and over half who had fibrinogen administered (58.3%; n=7 of 12).

Table 39: Drugs and Volume Replacement Day 1, 2 & 3 in 2019

	Day 1	Day 2	Day 3
Sedation	69(95.8)	64(88.9)	58(80.6)
Antibiotics	72(100)	58(80.6)	33(45.8)
Anticonvulsants	28(38.9)	20(27.8)	16(22.2)
Inotropes	18(25.0)	13(18.1)	8(11.1)
Blood products	12(16.7)	2(2.8)	4(5.6)
Volume replacement (normal saline)	18(25.0)	9(12.5)	4(5.6)
Other	20(27.8)	8(11.1)	5(6.9)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

One third of the infants who received TH in 2019 had an echocardiogram during their hospital admission (34.7%; n=25). All infants had microbiology bloods undertaken (100%; see Table 40). Four of the 72 infants had genetic bloods undertaken (5.6%).

Table 40: Investigations undertaken in 2019

	TH Cases N=72 2019
Echocardiogram	25(34.7)
Lumbar puncture	15(20.8)
Microbiology bloods	72(100)
Genetic bloods	4(5.6)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

Over the course of treatment, the median fluid input in milligrams per kg was 48.0 (Range 26-107) on Day 1, 50.0 (Range 15-71) on Day 2 and 50.0 (Range 34-94) on Day 3. The lowest blood sugar level reported was between 0 and 3 for a third of infants on Day 1 (38.9%; n=28), Day 2 (30.6%, n=22) and Day 3 (31.9%; n=23). Sodium levels were 131 or lower for two thirds of infants on Day 1 (65.3%; n=47), over half of infants on Day 2 (56.9%, n=41) and 43.1% of infants on Day 3 (n=31).

Table 41: Laboratory Parameters Day 1, 2 & 3 in 2019*

	Day 1	Day 2	Day 3
Coagulation	23(31.9)	9(9.7)	1(1.4)
Blood sugars			
0-3	28(38.9)	22(30.6)	23(31.9)
4-7	37(51.4)	38(52.8)	32(44.4)
≥8	5(6.9)	3(4.2)	3(4.2)
Not documented	2(2.8)	9(12.5)	14(19.4)
Sodium			
≤131	47(65.3)	41(56.9)	31(43.1)
132-136	18(25.0)	16(22.2)	18(25.0)
≥137	6(8.3)	6(8.3)	8(11.1)
Not documented	1(1.4)	9(12.5)	15(20.8)

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive. *Data for laboratory tests which may have been undertaken during assessment for TH were not recorded and therefore are not presented here

In relation to neuroimaging, 73.6% (n=53) of infants had a cranial ultrasound (Table 42) that occurred between Day 1 and Day 8 of life. Of the 53 cranial ultrasounds undertaken, 13 (24.5%) were reported as abnormal and five were reported to have increased echogenicity (9.4%).

Table 42: Cranial ultrasound undertaken in 2019

	Day 1 N=72	Day 2 N=72	Day 3 N=72	Day 4 or later N=72
Cranial ultrasound*	19(26.4)	19(26.4)	7(9.7)	6(8.3)

Note: Values are shown as N(%) unless otherwise stated. *Missing day of investigation for two infants

SARNAT Scoring

A diagnosis of encephalopathy, consisting of an altered state of consciousness (lethargy, stupor or coma) was only assigned to 65.3% (n=47 of 72) of infants who had a SARNAT completed on Day 1, for 48.4% (n=31 of 64) on Day 2 and 49.1% (n=29 of 59) of infants on Day 3. As outlined in Table 44, over a third were graded as severely encephalopathic on Day 1 (40.4%; n=19 of 44), Day 2 (38.7%; 12 of 31) and a quarter on Day 3 (24.1%; n=7 of 29) of treatment. Infants were assigned a SARNAT[23] score based on clinical behaviour on Day 1, Day 2 and Day 3 of treatment (Table 43).

Table 43: SARNAT Scoring on Treatment Day 1, 2 & 3 in 2019

		Day 1 N=72	Day 2 N=64	Day 3 N=59
Level of consciousness				
	Hyperalert	10(13.9)	5(7.8)	4(6.8)
	Lethargic or obtunded	33(45.8)	18(28.1)	23(39.0)
	Stupor or Coma	13(18.1)	10(15.6)	3(5.1)
	Normal	7(9.7)	12(18.8)	11(18.6)
	Undocumented	9(12.5)	19(29.7)	18(30.5)
Activity				
	Normal	16(22.2)	13(20.3)	14(23.7)
	Decreased	31(43.1)	23(35.9)	25(42.4)
	Absent	14(19.4)	8(12.5)	3(5.1)
	Undocumented	9(12.5)	20(31.3)	17(28.8)

Neuromuscular Control				
Muscle tone	Normal	12(16.7)	3(4.7)	10(17.0)
	Mild hypotonia	30(41.7)	15(23.4)	14(23.7)
	Flaccid	15(20.8)	10(15.6)	5(8.5)
	Undocumented	15(20.8)	33(51.6)	30(50.8)
Posture	Mild distal flexion	12(16.7)	5(7.8)	8(13.6)
	Strong distal flexion	11(15.3)	2(3.1)	5(8.5)
	Intermittent decerebration	10(13.9)	7(10.9)	2(3.4)
	Normal	12(16.7)	6(9.4)	4(6.8)
	Undocumented	27(37.5)	44(68.8)	40(67.8)
Stretch reflexes	Overactive	5(6.9)	4(6.3)	7(11.9)
	Decreased or absent	15(20.8)	7(10.9)	3(5.1)
	Normal	15(20.8)	6(8.3)	7(11.9)
	Undocumented	37(51.4)	46(63.9)	40(67.8)
	Deferred	0(0.0)	1(1.6)	2(3.4)
Complex Reflexes				
Suck	Weak	15(20.8)	10(15.6)	8(13.6)
	Weak or absent	12(16.7)	3(4.7)	9(15.3)
	Absent	13(18.1)	8(12.5)	4(6.8)
	Normal	10(13.9)	5(7.8)	8(13.6)
	Undocumented	20(27.8)	38(59.4)	30(50.8)
	Deferred	2(2.8)	0(0.0)	0(0.0)
Moro	Strong; low threshold	2(2.8)	1(1.6)	0(0.0
	Weak; incomplete high threshold	4(5.6)	1(1.6)	2(3.4)
	Absent	6(8.3)	1(1.6)	1(1.7)
	Normal	4(5.6)	1(1.6)	4(5.1)
	Undocumented	49(68.1)	55(85.9)	49(83.1)
	Deferred	7(9.7)	5(7.8)	4(6.8)
Tonic Neck	Slight	2(2.8)	0(0.0	0(0.0)
	Strong	3(4.2)	0(0.0)	0(0.0)
	Absent	0(0.0)	0(0.0)	1(1.7)
	Normal	2(2.8)	0(0.0)	1(1.7)
	Undocumented	64(88.9)	62(96.9)	55(93.2)
	Deferred	1(1.4)	2(3.1)	2(3.4)
Autonomic Function				
Pupils	Dilated	1(1.4)	1(1.6)	0(0.0)
	Constricted	18(25.0)	8(12.5)	10(16.9)
	Variable; often unequal, poor light reflex, fixed, dilated	8(11.1)	4(6.3)	3(5.1)
	Normal	17(23.6)	9(14.1)	8(13.6)
	Undocumented	28(38.9)	42(65.6)	38(64.4)
Heart rate	Tachycardia	5(6.9)	1(1.6)	2(3.4)
	Bradycardia	10(13.9)	11(17.2)	6(10.2)
	Variable	2(2.8)	2(3.1)	1(1.7)
	Normal	45(62.5)	43(67.2)	44(74.6)
	Undocumented	10(13.9)	7(10.9)	6(10.2)
Respiratory rate	Regular	19(26.4)	22(34.4)	22(37.3)
	Periodic breathing	21(29.2)	20(31.3)	16(27.1)
	Aponea	21(29.2)	14(21.9)	9(15.3)
	Normal	7(9.7)	5(7.8)	9(15.3)
	Not documented	4(5.6)	3(4.7)	3(5.1)
Seizures	None	41(56.9)	42(65.6)	42(71.2)
	Common; focal or multifocal	20(27.8)	9(14.1)	6(10.2)
	Uncommon (excluding decerebration)	5(6.9)	7(10.9)	2(3.4)
	Normal	4(5.6)	4(6.3)	6(10.2)
	Undocumented	2(2.8)	2(3.1)	3(5.1)

Note: Values are shown as N(%) unless otherwise stated

Table 44: Grade of Encephalopathy on Treatment Day 1, 2 & 3 in 2019

	Day 1 N=47	Day 2 N=31	Day 3 N=29
Mild	10(21.3)	5(16.1)	4(13.8)
Moderate	18(38.3)	14(45.2)	18(62.1)
Severe	19(40.4)	12(38.7)	7(24.1)

Note: Values are shown as N(%) unless otherwise stated

Over the course of the 72 hours of treatment, amplitude-integrated electroencephalography (aEEG) interpretation was documented for almost two thirds of cases on Day 1 (61.1%; n=44), half of cases on Day 2 (48.6%; n-35) and 41.7% of cases on Day 3 (n=30). Electrical seizures were identified in 21 of the 72 infants (29.2%) on Day 1, 11 of the infants (15.3%) on Day 2 and three of all 72 infants (4.2%) on Day 3 (Table 45).

Table 45: aEEG interpretation on Treatment Day 1, 2 & 3 in 2019

	Day 1 N=72	Day 2 N=72	Day 3 N=72
Background activity	**44(61.1)**	**35(48.6)**	**30(41.7)**
Normal	21 of 44(47.7)	15 of 35(42.9)	16 of 30(53.3)
Abnormal	8 of 44(18.2)	4 of 35(11.4)	1 of 30(3.3)
Moderately abnormal	6 of 44 (13.6)	5 of 35(14.3)	2 of 30(6.7)
Severely abnormal	2 of 44(4.5)	3 of 35(8.6)	1 of 30(3.3)
Not documented	35(48.6)	45(62.5)	52(72.2)
Sleep wake cycle			
Present	8 of 44(18.2)	8 of 35(22.9)	14 of 30(46.7)
Absent	6 of 44(13.6)	7 of 35(20.0)	4 of 30(13.3)
Not documented	30 of 44(68.2)	20 of 35(57.1)	12(40.0)
Electrical seizures	**21(29.2)**	**11(15.3)**	**3(4.2)**

Rewarming

Of the 72 infants who underwent TH treatment, 13 infants (18.1%) did not complete 72 hours of TH in 2019. As outlined in Table 46, two-thirds of these infants had their care redirected (66.7%; n=8 of 12; missing data for one infant).

Table 46: Indications to cease TH intervention in infants who underwent TH in 2016-2019 before 72 hours completed therapy

	TH cases N=4 2016	TH cases N=9 2017	TH cases N=8* 2018	TH cases N=12* 2019	TH cases N=33 2016-2019
Redirection of care	3(75.0)	7(77.8)	5(62.5)	8(66.7)	23(69.7)
PPHN	1(25.0)	1(11.1)	2(25.0)	3(25.0)	7(21.2)
Sepsis	0(0.0)	1(11.1)	1(12.5)	0(0.0)	2(6.1)
Cooling criteria not met	0(0.0)	0(0.0)	0(0.0)	1(8.3)	1(3.0)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for one infant

Excluding the 13 infants whose treatment was ceased, data on rewarming was available for 59 of the infants (100%). As outlined in Table 47, the majority of infants were rewarmed within 12 hours (91.5%; n=54 of 59) in 2019. During the rewarming period, three of the 59 infants (5.1%) had seizures. Infants were rewarmed over periods of between 1 and 16 hours.

Table 47: Duration of rewarming for infants who underwent therapeutic hypothermia in 2016-2019

	TH cases N=59 2016	TH cases N=66 2017	TH cases N=57 2018	TH cases N=59 2019	TH cases N=241 2016-2019
Up to 12 hours	48(81.4)	50(75.8)	49(86.0)	54(91.5)	197(81.7)
13 – 15 hours	4(6.8)	0(0.0)	1(1.8)	3(35.1)	8(3.3)
16 – 18 hours	7(11.9)	14(21.2)	7(12.3)	2(3.4)	30(12.4)
Greater than 19 hours	0(0.0)	2(3.0)	0(0.0)	0(0.0)	2(0.8)

Note: Values are shown as N(%) unless otherwise stated

Feeding

Data on the introduction of feeding was recorded for 59 of the 72 infants who underwent TH treatment (81.9%). The majority of infants reached full oral requirement (98.3%; n=58 of 59). Ten of the mothers breastfed on introduction of feed (16.9%), almost two-thirds of infants were fed with expressed breastmilk (61.0%; n=36 of 59) and 13 were fed with formula (22.0%). Data on the day infants who underwent TH had feed introduced was recorded for 58 of the 72 infants. As outlined in Table 48, the majority of infants had feed introduced on Day 4 (48.3%; n=28 of 58) or Day 5 (22.4%; n=13 of 58).

Table 48: Age that infants who underwent therapeutic hypothermia in 2016-2019 had feed introduced

	TH cases N=60 2016	TH cases N=66 2017	TH cases N=63 2018	TH cases N=58 2019	TH cases N=247 2016-2019
Up to Day 3	6(10.0)	2(3.0)	11(17.5)	7(12.1)	26(10.5)
Day 4	17(28.3)	21(31.8)	33(52.4)	28(48.3)	99(40.1)
Day 5	25(41.7)	28(42.4)	15(23.8)	13(22.4)	81(32.8)
Day 6	8(13.3)	11(16.7)	3(4.8)	7(12.1)	29(11.7)
Day 7+	4(6.6)	4(6.1)	1(1.6)	3(5.2)	12(4.9)

Note: Values are shown as N(%) unless otherwise stated

Of these 59, three-quarters of infants were initially fed with a nasogastric tube (78.0%; n=46). Of these, one quarter of infants were fed with a nasogastric tube for between 24 hours and 47 hours (25.0%; n= 9 of 36; missing data for 10 infants). As indicated in Table 49, one infant was discharged home with a nasogastric tube (2.8%).

Table 49: Duration of feeding with a nasogastric tube for infants who underwent therapeutic hypothermia in 2016-2019

	TH cases N=30 2016	TH cases N=36 2017	TH cases N=34 2018	TH cases N=36 2019	TH cases N=126 2016-2019
Less than 24 hours	9(30.0)	7(19.4)	8(23.5)	6(16.7)	30(23.8)
24-47 hours	6(20.0)	7(19.4)	3(8.8)	9(25.0)	25(19.8)
48-71 hours	4(13.3)	8(22.2)	1(2.9)	9(25.0)	22(17.5)
Greater than 72 hours	8(26.7)	6(16.7)	21(61.8)	11(30.6)	36(28.6)
Discharged home with a nasogastric tube	3(10.0)	8(22.2)	1(2.9)	1(2.8)	13(10.3)

Note: Values are shown as N(%) unless otherwise stated

Specific placental conditions

Of the 72 infants who underwent TH, the placenta was retained and sent for histological analysis in 53 of the 72 cases (73.6%). Of these, 49 placental examinations were complete (92.5%, n=49 of 53, Table 50). All 49 completed reports were made available to the NPEC for inclusion in this report.

Placental disease categories have been divided into subsections and, while numbers in any one year are small, it will assist in understanding the relative contribution of placental conditions. In particular, a severe fetal inflammatory response is associated with abnormal neonatal neurologic findings in cases of chorioamnionitis.

Abnormal placental findings have been classified in line with recommendations from the publication from the international consensus meeting of pathology[9]. These are presented under the following broad categories: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), cord pathology, cord pathology with distal disease, chorioamnionitis, villitis and other.

Analysis of placentas from infants treated with TH has shown broadly similar findings to previous years, although maternal vascular malperfusion (MVM) shows reduced numbers. MVM, previously classified as uteroplacental ischaemia (UPI) is the most common pathology identified in stillbirths and in previous reports on TH placentas for 2016-18. The submission rate of placentas for TH, at 68.1% (n=49 of 72), may be in part responsible for this.

Two categories previously subsumed into the category of "other" have been listed separately this year. Delayed villous maturation renders term infants more susceptible to hypoxia. It may co-exist with and in some cases be secondary to impairment in fetoplacental flow (fetal vascular malperfusion, FVM). An important finding is meconium-associated vascular necrosis (MAVN). This is where meconium passed by the fetus is associated with death of smooth muscle cells in the cord or on the chorionic plate, possibly causing vasospasm and thereby worsening hypoxia. It would usually be seen in <1/1000 deliveries, and its presence here in 3 of 49 cases deserves scrutiny.

With the increasing use of the Amsterdam criteria[9] for placental reporting, the potential for exploration of the associations of placental pathology, neonatal course and developmental outcome is enhanced. It is therefore critically important that placental submission rates in TH reach if not exceed the excellent rates of >95% achieved for stillbirth.

Table 50: Placental histology findings for infants who underwent neonatal therapeutic hypothermia in 2016-2019 versus Stillbirths in 2017

	TH cases N=72 2016/2017	TH cases N=41 2018	TH cases N=49 2019	Stillbirth[16] N=234 2017
Maternal Vascular Malperfusion (MVM)	19(26.4)	12(29.2)	6(12.2)	81(34.6)
• Low Grade		11(26.8)	2(4.1)	
• High Grade		1(2.4)	4(8.2)	
Fetal Vascular Malperfusion (FVM)	16(22.2)	7 (17.0)	4(8.2)	60(25.6)
• Low Grade		4(9.7)	1(2.0)	
• High Grade		3(7.3)	3(6.1)	
Any Cord Pathology	14(19.4)	14 (34.0)	17(34.7)	54(23.1)
• Isolated		9(21.9)	12(24.5)	
• Cord Pathology with distal FVM		3 (7.3)	3(6.1)	
• Cord Pathology with distal High Grade FVM		2 (4.8)	2(4.1)	
Chorioamnionitis	20(27.8)	14(34.1)	10(20.4)	21(9.0)
Chorioamnionitis FIR Stage 2		1(2.4)	0(0.0)	
Villitis	3(4.2)	4(9.7)	6(12.2)	10(4.3)
Other Placental Condition	28(38.9)	12(29.2)	13(26.5)	35(15.0)
• Other			6(12.2)	
• Delayed Villous Maturation			4(8.2)	
• Meconium-associated Vascular Necrosis			3(6.1)	
Normal	–	3(7.3)	8(16.3)	–

Note: Values are shown as N(%) unless otherwise stated. Categories are not mutually exclusive

Discharge diagnosis and neonatal death

Of the 72 infants who underwent TH treatment, 60 infants had an MRI of the brain undertaken of which 58 infants (80.5%) had an MRI report available. One quarter of infants had an MRI on day 5 of life (25.4%; n=15 of 59). One in ten infants had an MRI between day 10 and 15 of life (10.2%; n=6 of 59; see Table 51).

The 58 available MRI reports were assessed by adopting the Barkovich scoring system in HIE[24]. Adopting the Barkovich HIE scoring system, almost one third had an abnormal MRI (31.0%; n=18 of 58) compared to 25.4% (n=15 of 59) of the infants in 2018 with an abnormal report. The full set of Barkovich HIE scores for infants with an abnormal result in 2019 are outlined in Appendix E .

Table 51: Day of life MRI undertaken in 2019

	TH Cases N=59* 2019
1-4	9(15.3)
5	15(25.4)
6	12(20.3)
7	3(5.1)
8	9(15.3)
9	5(8.5)
10-15	6(10.2)

Note: Values are shown as N(%) unless otherwise stated. *Missing data for one infant

There was a grade of encephalopathy documented for the majority of the 58 infants who were discharged (89.7%; n=52 of 58). The overall grade of encephalopathy assigned to an infant during their admission is the worst grade of encephalopathy achieved during admission. When a grade was referenced at discharge, a grade of moderate encephalopathy was assigned to over half of cases (57.7%; n=30 of 52; undocumented for 6). One in seven infants had a grade of mild on discharge (15.4%, 8 of 52; undocumented for 6).

Table 52: Grade of encephalopathy on discharge in 2016-2019

	TH cases N=60 2016	TH cases N=68 2017	TH cases N=69 2018	TH cases N=58 2019	TH cases N=255 2016-2019
HIE – no grade assigned	27(45.0)	29(42.6)	0(0.0)	0(0.0)	56(21.9)
Mild HIE	2(3.3)	3(4.4)	4(5.8)	8(13.8)	17(6.7)
Mild-Moderate HIE	1(1.7)	6(8.8)	4(5.8)	6(10.3)	17(6.7)
Moderate HIE	23(38.3)	18(26.5)	31(44.9)	30(51.7)	102(40.0)
Moderate to Severe HIE	0(0.0)	1(1.5)	3(4.3)	1(1.9)	5(2.0)
Severe HIE	6(10.0)	5(7.4)	15(21.7)	7(13.5)	33(12.9)
HIE not documented	1(1.7)	6(8.8)	12(17.4)	6(10.3)	25(9.8)

Note: Values are shown as N(%) unless otherwise stated

The survival rate for the infants who underwent TH in 2019 was 79.2%, as 15 of the 72 infants died. Twelve of deaths occurred within 7 completed days of birth and were classified as early neonatal deaths (80.0%; n=12 of 15). As outlined in Table 53, three deaths occurred after the 7th day and within 28 completed days of birth and were classified as late neonatal deaths (20.0%; n=3 of 15). Fourteen of the infants were referred to the coroner (93.3%) and 13 infants had an autopsy performed (86.7%). It is important to note that data on the findings of these reports, and on the infants' respective causes of death, were not collected for this report.

Table 53: Perinatal and infant mortality for infants who underwent therapeutic hypothermia in 2016-2019

	TH cases N=6 2016	TH cases N=11 2017	TH cases N=7 2018	TH cases N=15 2019	TH cases N=39 2016-2019
Early neonatal death	0(0.0)	5(45.5)	3(42.9)	12(80.0)	20(51.3)
Late neonatal death	2(33.3)	4(36.4)	3(42.9)	3(20.0)	12(30.8)
Infant death	4(66.7)	2(18.2)	1(14.3)	0(0.0)	7(17.9)

Note: Values are shown as N(%) unless otherwise stated

As outlined in Table 54, first infant blood lactate level was strongly associated with risk of death among infants treated with TH. As expected, infants with a higher blood lactate were at a higher risk of death. The continued need for PPV or intubation at 10 mins was also strongly associated with mortality with these infants being 6.9 times more at risk. Infants with a base deficit greater than 16.0 mmol/L in umbilical cord, or any blood sample, within 60 minutes of birth had 4.9 times higher risk of death compared to the other infants. Similarly, low Apgar score was an indicator of mortality risk. Twenty-one percent of the infants with an Apgar score ≤5 at 10 minutes died, which was 4.8 times higher than the risk of deaths compared to the other infants.

Table 54: Maternal and infant characteristics and mortality risk for infants who underwent therapeutic hypothermia in 2016-2019

		Number of infants	Number (%) who died	Risk ratio
All		281	39(13.9)	
Parity	Nulliparous	166	21(12.7)	1.00 (ref.)
	Parous	115	18(15.7)	1.24
Mode of delivery	Vaginal delivery	67	10(14.9)	1.00 (ref.)
	Instrumental	92	6(6.5)	0.44
	CS pre labour	59	14(23.7)	1.59
	CS after the onset of labour	63	9(14.3)	0.96
Birthweight centile	<10th	49	6(12.2)	1.57
	10-49th	112	23(20.5)	2.64
	50-89th	90	7(7.8)	1.00 (ref.)
	>90th	30	3(10.0)	1.29
Sex	Male	158	17(10.8)	1.00 (ref.)
	Female	123	22(17.9)	1.66
First infant blood lactate	0 to 4	30	1(3.3)	0.76
	5 to 14	137	6(4.4)	1.00 (ref.)
	15+	79	20(25.3)	5.78
	Undocumented	35	12(34.3)	7.83
Assessment for TH				
>36 completed weeks gestational age	Yes	273	39(14.3)	1.00 (ref.)
	No	8	0(0.0)	0.00
Apgar score ≤5 at 10 minutes	Yes	135	34(25.2)	7.25
	No	144	5(3.5)	1.00 (ref.)
Weight ≥1800 grams	Yes	278	29(14.0)	1.00 (ref.)
	No	3	0(0.0)	0.00
Continued need for PPV or Intubation at 10 mins	Yes	177	35(19.8)	6.79
	No	103	3(2.9)	1.00 (ref.)
Did an acute perinatal event occur?	Yes	172	28(16.3)	1.61
	No	109	11(10.1)	1.00 (ref.)
Acidosis present in umbilical cord, or any blood sample within 60 minutes of birth	Yes	187	35(18.7)	4.40
	No	94	4(4.3)	1.00 (ref.)
Base Deficit >16.0 mmol/L in umbilical cord, or any blood sample, within 60 minutes of birth	Yes	142	31(21.8)	4.95
	No	136	6(4.4)	1.00 (ref.)
Diagnosis of encephalopathy during assessment for TH	Yes	200	30(15.0)	1.35
	No	81	9(11.1)	1.00 (ref.)

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)

Table 55: Bayley III scores for TH (N=40)

Bayley III	Total (n=40)	Normal MRI Outcome (n=11)	Abnormal MRI Outcome (n=6)
Cognitive Composite Score*			
Mean (SD)	103.6 (13.4)		
Range	70-30		
• Above average (≥110)	13 (33.3)	5 (45.5)	1 (16.7)
• Normal range (90-109)	21 (53.8)	6 (54.5)	4 (66.7)
• Mild/Moderate Delay (70-89)	5 (12.9)	0 (0.0)	1 (16.7)
• Extremely Delay (≤69)	0 (0.0)	0 (0.0)	0 (0.0)
Language Composite Score			
Mean (SD)	99.1 (16)		
Range	74-32		
• Above average (≥110)	8 (20.0)	4 (36.4)	1 (16.7)
• Normal range (90-109)	22 (55.0)	5 (45.5)	1 (16.7)
• Mild/Moderate Delay (70-89)	10 (25.0)	2 (18.2)	4 (66.7)
• Extremely Delay (≤69)	0 (0.0)	0 (0.0)	0 (0.0)
Motor Composite Score			
Mean (SD)	99.2 (15)		
Range	67-139		
• Above average (≥110)	9 (22.5)	5 (45.5)	1 (16.7)
• Normal range (90-109)	25 (62.5)	6 (54.5)	4 (66.7)
• Mild/Moderate Delay (70-89)	4 (10.0)	0 (0.0)	1 (16.7)
• Extremely Delay (≤69)	2 (5.0)	0 (0.0)	0 (0.0)
Cognitive Scaled Score**			
Mean (SD)	10.9 (2.6)		
Range	4-16		
• 1SD above (≥13)	10 (27.0)	4 (40.0)	1 (20.0)
• Normal range (8-12)	23 (62.2)	6 (60.0)	4 (80.0)
• 1SD below (≤7)	4 (10.8)	0 (0.0)	0 (0.0)
Receptive Communication (RC) Scaled Score			
Mean (SD)	10.1 (3.1)		
Range	4-16		
• 1SD above (≥13)	10 (25.0)	4 (36.4)	1 (16.7)
• Normal range (8-12)	25 (62.5)	6 (54.5)	4 (66.7)
• 1SD below (≤7)	5 (12.5)	1 (9.1)	1 (16.7)
Expressive Communication (EC) Scaled Score			
Mean (SD)	9.5 (2.8)		
Range	5-15		
• 1SD above (≥13)	7 (17.5)	3 (27.3)	1 (16.7)
• Normal range (8-12)	24 (60.0)	6 (54.5)	1 (16.7)
• 1SD below (≤7)	9 (22.5)	2 (18.2)	4 (66.7)

Fine Motor (FM) Scaled Score			
Mean (SD)	10.8 (3)		
Range	4-19		
• 1SD above (≥13)	9 (22.5)	6 (54.5)	0 (0.0)
• Normal range (8-12)	27 (67.5)	5 (45.5)	5 (83.3)
• 1SD below (≤7)	4 (10)	0 (0.0)	1 (16.7)
Gross Motor (GM) Scaled Score			
Mean (SD)	9.2 (2.8)		
Range	3-17		
• 1SD above (≥13)	5 (12.5)	2 (18.2)	1 (16.7)
• Normal range (8-12)	26 (65.0)	8 (72.7)	3 (50.0)
• 1SD below (≤7)	9 (22.5)	1 (9.1)	2 (33.3)

Note: Values are shown as N(%) unless otherwise stated.SD (Standard Deviation). *One missing case. **Three missing cases

The BSID-III is an individually administered test instrument to assess the developmental functioning of infant to toddler and young children between 1 and 24 months. The BSID-III provides standardised outcome composite scores for the following domains: cognitive, language and motor development. The scale also provides standardised scaled score outcomes for cognitive development, receptive communication, expressive communication, fine motor and gross motor development. These scaled scores facilitate the examiner in determining specific delays such as expressive communication or gross motor delay while receptive communication and fine motor development could be normal.

As outlined in Table 55, the composite scores and scaled scores are presented for a cohort of 40 children who were treated with TH at birth and assessed at 2 years of age using the BSID-III[22]. The categories used to represent the composite score outcomes across the cohort have been divided into the following: Above Average, Average, Mild/Moderate Delay and Extremely delayed performance using the Bayley Manual classifications[25]. These classifications demonstrate a broad range of outcomes. Children performing within the mild delayed range would be expected to benefit from appropriate and tailored intervention thus improving their outcome over time while children performing within the moderate and extremely delayed categories will still face many developmental challenges[25].

Scaled scores have also been presented for each domain as these facilitate further breakdown of the results, for example, for the language scale we can now look at receptive communication and expressive communication skills separately. For the motor scale we can measure fine motor and gross motor separately. These standardised scaled scores have been very helpful to clinicians in terms of determining the type of intervention required to address the delay. These scaled scores have been broken down to measure High Average (1SD above the mean), Average and Delayed (1 SD below the mean) performance in accordance with the Bayley III Manual classification[25].

The Mean scores, Standard Deviations (SD) and Ranges have been calculated for all domains within the group. The results show us that 33.3% (n=13) of children scored above average for the Composite Cognitive domain compared to 20.0% (n=8) and 22.5% (n=9) respectively for the Composite Language and Motor domains. Average outcome scores for the Composite Cognitive and Language domains were measured at 53.8% (n=21) and 55.0% (n=22) while average outcomes for the motor composite was 62.5% (n=25). There were two extremely delayed outcomes reported for the Composite Motor domain with no reported cases for the Composite Cognitive and Language domains. However, 25.0% (n=10) of children demonstrated mild/moderate language delay. When this delay was examined further 22.5% (n=9) of children demonstrated performance at 1 SD below the mean for the scaled score for Expressive Communication higher than the Receptive Communication domain at 12.5% (n=5). 22.5% (n=9) of children demonstrated performance at 1 SD below the mean for the scaled score for Gross Motor development higher percentage of delay than for the Fine Motor domain at 10% (n=4).

Approximately 10% (n=4) of the TH cases that performed the BSID-III scores had abnormal results for the three composite scores, cognitive, language and motor. Two of them had a score equal or less than 69 for the motor composite score. Almost 70% (n=27) of these cases had a normal score for the three composite scores, cognitive, language and motor. Of the eight remaining cases, seven had at least two normal composite scores and one had only one normal language composite score.

OBSTETRIC CASE REVIEW TOOL

To investigate the obstetric antecedents of an infant requiring therapeutic hypothermia intervention.

When reviewing cases of neonatal encephalopathy, the following types of data may be helpful to identify learning.

- MATERNAL DEMOGRAPHICS
- PREVIOUS PREGNANCY HISTORY
- CURRENT PREGNANCY HISTORY
- ANTENATAL RISK ASSESSMENT (including not undertaken)

SENTINEL EVENTS

Placental Abruption

Consider risks/aetiology – Previous abruption, hypertension, abdominal trauma, smoker, drug misuse.

Uterine Rupture

History of previous caesarean section or other uterine surgery. Was oxytocin/prostaglandin used?

Shoulder Dystocia

Consider risks/aetiology – History of shoulder dystocia, BMI, diabetes, macrosomia, failure to progress in labour.

Cord Prolapse

Consider risks/aetiology – Abnormal presentation, unstable lie, ARM?

Maternal Collapse

Consider aetiology – Eclampsia, seizure, myocardial infarction, anaesthetic event, amniotic fluid embolus, etc.

Fetal Haemorrhage

Consider aetiology placenta previa, vasa previa, trauma, placental cause etc.

RECURRING FACTORS

Cardiotocograph Monitoring

Consider use and findings – Adequate monitoring, appropriate quality of trace, suspicious features, second eyes/second review/opinion undertaken, documented training of attending medical/midwifery personnel.

Oxytocin

Consider use/misuse; tachyphylaxis, hyper stimulation, medical review of inadequate progress, response, etc.

Communication

Assess presence or absence of good practice as documented – Second eyes, documentation of maternal concerns, concerns escalated appropriately to senior midwifery/ senior medical staff, appropriate staff: patient ratios.

Pyrexia/PROM

Consider factors such as – Appropriate review, assessment and investigation, care plan, appropriate antibiotic therapy, was there an indication for urgent delivery, etc.

Failure to Progress

Consider risks/aetiology – Nulliparous or parous mother, abnormal presentation, primary or secondary FTP, issues with maternal care plan, appropriate escalation, appropriate medical response, etc.

Diagnosis of Labour

Consider diagnosis of labour, timing – Did mother self-present, time after admission diagnosis of labour made, appropriate monitoring, etc.

Induction

Consider documentation – Indication and plan for induction, cervical assessment at time of planning, indication discussed with consultant if not per guideline. Consultant informed if cervix unfavourable and kept updated.

Instrumental

Delivery done by appropriate grade of doctor? Decision and timing of events documented, procedure(s) well documented, consequences of repeated attempts considered and understood.

Document the review team including their discipline, specialty and grade.

Not every case that requires TH will be covered by this review – the above events and factors will cover the majority.

National Women & Infants Health Programme

Seirbhís Sláinte Níos Fearr á Forbairt | Building a Better Health Service

NATIONAL PERINATAL EPIDEMIOLOGY CENTRE

Gníomhaireacht Bainistíochta an Chisteáin Náisiúnta
National Treasury Management Agency

An Ghníomhaireacht um Éilimh ar an Stát
State Claims Agency

CANDIDACY CHECKLIST FOR NEONATAL THERAPEUTIC HYPOTHERMIA (COOLING)

PATIENT'S NAME: _____ **HOSP. NO:** _____

TIME of BIRTH: _____:_____ **hrs.** **CURRENT AGE in hours /minutes:** _____ **hrs.**_____**mins.**

If current age is greater than 6 hours, call tertiary cooling centre before proceeding.

Directions for the use of this checklist: Start at the top and work through each numbered component. When directed to proceed to the exam (neurological criteria), refer to the exam found on page 2. If there is missing data, (such as Apgar scores) and you are in doubt as to whether or not the patient qualifies for cooling, consult with the tertiary cooling centre promptly to discuss the patient.

Clinical Information	Criteria *(place a tick in the box that corresponds to the patient information)*	Instructions
Gestation	1 ≥ 36 weeks gestation ☐	Go to → 2 **Weight**
	= 35 weeks gestation ☐	May not be eligible *Contact cooling centre*
	< 35wks gestation ☐	Not Eligible
Weight	2 ≥ 1800 grams ☐	Go to → 3 **Blood Gas**
	< 1800 grams ☐	Not Eligible
Blood Gas pH = _____ Base Deficit = _____ Source: Cord ☐ Or 1st infant blood gas at <1hour of life ☐ Arterial ☐ Capillary ☐ Venous Time Obtained: _____:_____	3 pH < 7.0 ☐ or Base Deficit ≥ 16 ☐	Criteria met thus far. Go to **EXAM***
	No gas obtained ☐ or pH ≥ 7.0 ☐ or Base Deficit < 16 ☐	May not be eligible; Go to → 4 **History of acute perinatal event**
Acute Perinatal Event *(tick all that apply)*	4 Variable / late foetal HR decelerations ☐ Prolapsed / ruptured/tight nuchal cord ☐ Uterine Rupture ☐ Maternal haemorrhage / placental abruption ☐ Maternal trauma (eg. vehicle accident) ☐ Mother received CPR ☐	Any ticked, Go to → 5 **Apgar score**
	No perinatal event ☐ or Indeterminate what the event was because of home birth or missing information ☐	May not be eligible; Go to → 5 **Apgar score**
Apgar Score at 1 minute _____ 5 minute _____ 10 minute _____	5 Apgar ≤ 5 at 10 minutes ☐	Criteria met thus far. Go to **EXAM***
	Apgar > 5 at 10 minutes ☐	May not be eligible; Go to → 6 **Resuscitation after delivery**
Resuscitation after Delivery *(tick all that apply)* _____ PPV/intubated at 10 minutes _____ CPR _____ Adrenaline administered	6 Continued need for PPV or Intubated at 10 minutes? ☐	Criteria met thus far. Go to **EXAM***
	No PPV/not Intubated at 10 mins? ☐	Does not meet the current evidence based criteria for therapeutic hypothermia

Signature:_____ **Professional No.:**_____ **Date of Exam:**____/____/____ **Time of Exam:**____:____

Circle findings for each domain
PATIENT IS ELIGIBLE FOR COOLING WHEN 3 OR MORE DOMAINS HAVE FINDINGS IN COLUMNS 2 OR 3
Neurological criteria to be assessed between 1 and 6 hours after birth (Assessment of encephalopathy may be less accurate if performed prior to 1 hour of age)

Domain	1	2	3
Seizures	**No Seizures**	**Focal or Multifocal Seizures** (Multifocal: clinical activity involving > one site which is asynchronous and usually migratory) Note: If the patient is < 6 hours old and meets the gestation, weight and blood gas criteria and has a witnessed seizure, patient is eligible for cooling regardless of the rest of this exam	**Severe, Generalised Seizures** (Often resistant to conventional treatment) Note: If the patient is < 6 hours old and meets the gestation, weight and blood gas criteria and has a witnessed seizure, patient is eligible for cooling regardless of the rest of this exam
Level of Consciousness	**Normal** **or** **Hyperalert**	***Lethargic*** Decreased activity in an infant who is aroused and responsive **Definition of Lethargic:** • Sleeps excessively with occasional spontaneous eye opening • Responses are delayed but complete • Threshold for eliciting such responses increased • Can be irritable when disturbed	**Stuporous / Comatose** Demonstrates no spontaneous eye opening and is difficult to arouse with external stimuli **Definition of Stuporous:** • Aroused only with vigorous and continuous stimulation **Definition of Comatose:** • No eye opening or response to vigorous stimulation In both stupor and coma, the infant may respond to stimulation by grimacing/ stereotyped withdrawal / decerebrate posture
Spontaneous activity when awake or aroused	**Active** **Vigorous, doesn't stay in one position**	**Less than active, not vigorous**	**No activity**
Posture	**Moving around and does not maintain only one position**	**Distal flexion, complete extension or "frog-legged" position** Term infants with HIE often exhibit • Weakness in hip-shoulder distribution (eg proximal part of extremities) • Distal joints, fingers and toes often exhibit strong flexion • Thumbs strongly flexed and adducted. • Wrists often flexed • Above postures are enhanced by any stimulation	**Decerebrate with or without stimulation (all extremities extended)**
Tone	**Normal** • Resists passive motion **Hypertonic, jittery** • Lowered threshold to all types of minimal stimuli eg light touch, sudden noises • Infant may even respond to his/her own sudden movements	**Hypotonic or floppy,** • Axial hypotonia and/or limb hypotonia	**Completely flaccid**
Primitive reflexes	***Suck:*** Vigorously sucks finger or ETT ***Moro:*** Normal: Limb extension followed by flexion with stimulus	***Suck:*** Weak ***Moro:*** Incomplete	***Suck:*** Completely absent ***Moro:*** Completely absent
Autonomic system	***General Activation of Sympathetic nervous system*** ***Pupils:*** • Normal size (-1/3 of iris diameter) • Reactive to Light ***Heart Rate:*** • Normal, > 100bpm ***Respirations:*** • Regular spontaneous breathing	***General Activation of Parasympathetic nervous system*** ***Pupils:*** • Constricted (< 3mm estimated) • but reactive to light ***Heart Rate:*** • Bradycardia (< 100bpm, variable up to 120) ***Respirations:*** • Periodic, irregular breathing effort • Often have more copious secretions and require frequent suctioning	***Pupils:*** • Skew gaze, fixed, dilated, • not reactive to light ***Heart Rate:*** • Variable, inconsistent heart rate, irregular, may be bradycardic ***Respirations:*** • Completely apnoeic, requiring PPV & / or ET intubation and ventilation

Signature:_____ **Professional No.:**_____ **Date of Exam:** ____/____/____ **Time of Exam:** ____:____

This checklist, adapted from the 'STABLE Program', 6th edition, 2013, has been produced by the National Neonatal Transport Programme (NNTP) and endorsed by the Faculty of Paediatrics, Royal College of Physicians, Ireland. 1st edition, March 2014. This 2nd edition, July 2017. Also referenced: 1.*The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: A randomised controlled trial.* Dennis Azzopardi and The TOBY Study Group. BMC Pediatrics 2008, 8:17
2. *Optimizing Therapeutic Hypothermia for Neonatal Encephalopathy*. Steven L. Olsen et al. Pediatrics Feb 2013, 131 (2) e591-e603

Appendix C. Sarnat Teaching Cards

Modified Sarnat Staging for Neonatal Encephalopathy			
Severity	**Stage 1 (mild)**	**Stage 2 (Moderate)**	**Stage 3 (Severe)**
Level of consciousness	Hyperalert	Lethargic / Obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular Control:			
Muscle tone	Normal	Mild hypotonia/hypertonia	Flaccid/rigid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Tendon reflexes	Overactive	Overactive	Decreased or Absent
Complex reflexes			
Suck	Weak	Weak/absent	Absent
Moro	Strong, low threshold	Weak, incomplete,high threshold	Absent
Tonic neck	Slight	Strong	Weak or absent
Autonomic Nervous System			
Pupils	Dilated pupil	Constricted pupil	Variable: often unequal, poor light reflex, fixed, dilated
Heart rate	Tachycardia	Bradycardia	Variable
Respiratory rate	Regular	Periodic breathing	Apnoea
Seizure	None	Common; focal or multifocal	Uncommon (excluding decerebration)

Modified from Sarnat HB, Sarnat MS. Neonatal Encephalopathy Following Fetal Distress.A Clinical and Electroencephalographic Study. *Arch Neurol.* 1976;33(10):696–705

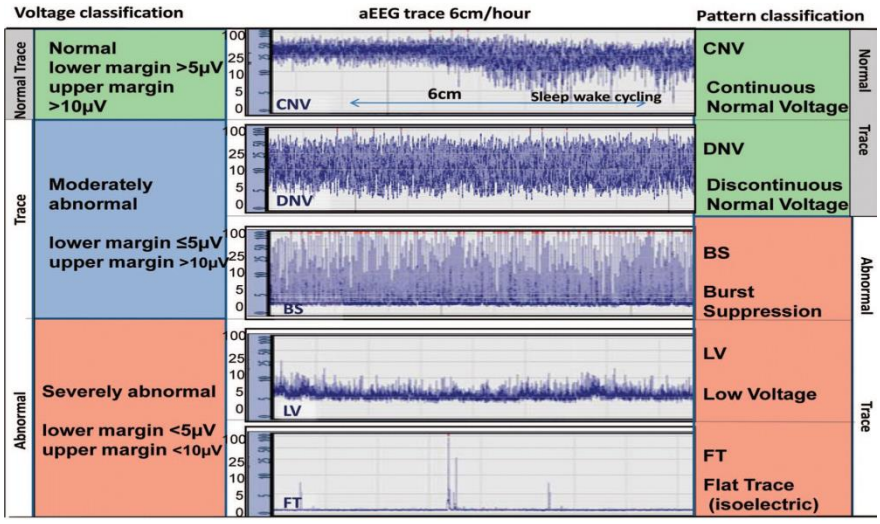
- ✓ **Key parameters to assess level of consciousness:** response to stimuli, corneal and gag reflex, motor activity
- ✓ **Stimulation technique:** Mild stimuli (tactile touch), Moderate stimuli (heel flick), Noxious stimuli (pinch of thumbnail/earlobe)

- **Hyperalert:** respond readily to stimuli, corneal and gag reflexes present, normal motor activity
- **Lethargy:** delayed response to stimuli, corneal and gag reflexes present, reduced motor activity
- **Obtunded:** delayed, incomplete response to stimuli, corneal and gag reflexes present, markedly reduced motor activity
- **Stupor**: only respond to strong noxious stimuli, Absent corneal and gag reflexes , no spontaneous motor activity, other – shallow ataxic breathing, apnoeic
- **Coma:** No response to noxious, vigorous stimulation, absent corneal and gag reflexes, no motor activity

- ➢ **Posture:** Normal posture = flexion and adduction of all limbs
- ➢ **Key deep tendon reflexes:** knee, supinator, biceps
- ➢ **Mean horizontal papillary diameter:** Term neonates: 3.8 mm +/- 0.8mm (SD)

Summary Document for aEEG Interpretation

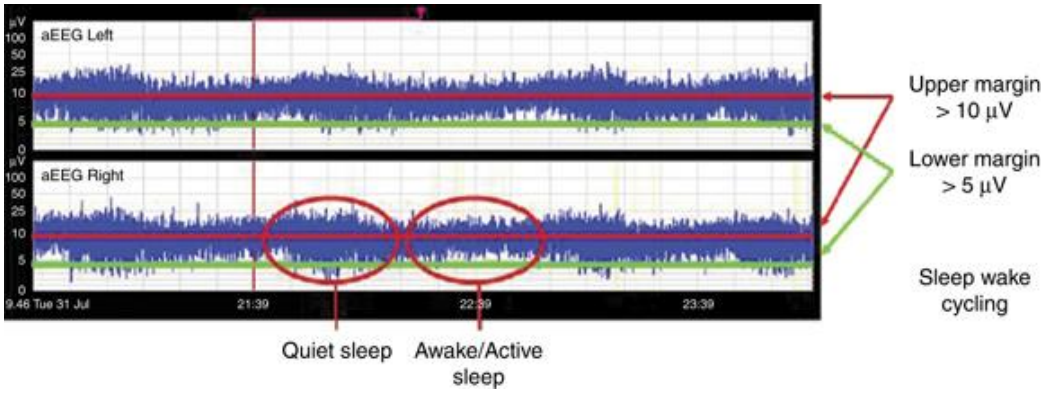
1. Background Voltage and Pattern Classification



From Thoresen M, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul;126(1):e131-9. PMID:9563847 Reprinted with permission of The American Academy of Pediatrics

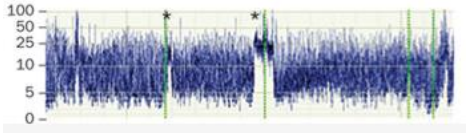
2. Presence of Sleep-Wake Cycling (SWC)

- SWC characterized by smooth sinusoidal variations, mostly in the minimum amplitude of the trace

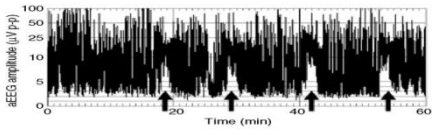


3. Presence of Seizures

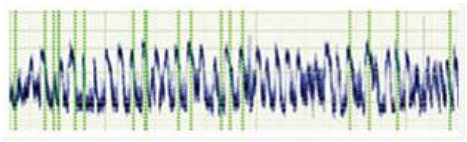
- Single seizure: solitary seizure



- Repetitive seizures: single seizures appearing more frequently than at 30 minute intervals



- Status Epilepticus: Continuous ongoing seizure activity for > 30 minutes



Appendix E. Barkovich Scoring in HIE

Result	Watershed (WS)	Basal Ganglia/Watershed (BG/W)	Basal Ganglia (BG)
Abnormal	1	2	0
Abnormal	5	4	2
Abnormal	2	2	0
Abnormal	0	1	2
Abnormal	0	1	4
Abnormal	0	1	1
Abnormal	0	1	2
Abnormal	4	2	0
Abnormal	1	2	0
Abnormal	2	2	0
Abnormal	1	0	0
Abnormal	2	3	1
Abnormal	5	4	4
Abnormal	2	2	0
Abnormal	0	1	1
Abnormal	3	3	4
Abnormal	0	1	3
Abnormal	4	2	0

Appendix F. Neonatal Therapeutic Hypothermia Working Group Members

Ms Ann Bowden, Co-ordinator, National Neonatal Transport Programme, Rotunda Hospital

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Coombe Women & Infants University Hospital;
Dr Martin White/ Ms Anne O'Sullivan

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Dr Peter Filan/ Ms Lucille Bradfield

Kerry General Hospital;
Dr Pervaiz/ Ms Maudie Creagh

Letterkenny General Hospital;
Dr Mathew Thomas/ Kathleen Greenough/
Ms Evelyn Smith

Mayo General Hospital;
Ms Andrea McGrail

Midland Regional Hospital, Mullingar;
Ms Geraldine Kavanagh

Midland Regional Hospital, Portlaoise;
Dr Gallagher/ Ms Yolanda Fennell

National Maternity Hospital;
Prof John Murphy/ Ms Julie McGinley

Our Lady of Lourdes Hospital, Drogheda;
Ms Claire Shannon

Portiuncula Hospital;
Ms Priscilla Neilan/ Ms Deirdre Naughton

Rotunda Hospital;
Prof Adrienne Foran/ Kathy Conway

Sligo University Hospital;
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Ms Maura Grogan

St. Luke's General Hospital, Kilkenny;
Ms Breda O'Dwyer

University Hospital Galway;
Ms Jean James/ Ms Aine Binchy

University Hospital Limerick;
Ms Margo Dunworth

University Hospital Waterford;
Ms Audrey Comerford/ Ms Paula Curtain

Wexford General Hospital;
Ms Helen McLoughlin

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